University of Alberta

Behavioral and Psychological Symptoms of Dementia:

Vocally Disruptive Behavior and a Review of Pharmacological Interventions.

by

Jason Spurrell

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of Master of Education
in

Psychological Studies in Education

Department of Educational Psychology

Edmonton, Alberta
Fall, 2008

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Your file Votre référence
ISBN: 978-0-494-47159-3
Our file Notre référence
ISBN: 978-0-494-47159-3

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Canada

For Jodie-

For believing that I can do anything.

For my parents and my grandmother-

For teaching me

the value of hard work and

the importance of an education.

Abstract

This study evaluated the psychotropic drug treatment of 19 participants with severe dementia that displayed vocally disruptive behavior (VBD). The participants that were discharged without mitigating circumstances were prescribed different combinations of atypical antipsychotics, antidepressants, benzodiazepines and anticonvulsants. Using these data and the mean rating of the day shift VDB, the present study could not find any relationship between VDB and a specific psychotropic medication. Screaming-VDB was more likely to be associated with a diagnosis of Dementia of the Alzheimer's Type (AD) and participants diagnosed with mixed dementia displayed significantly higher levels of VDB. A neurological/cognitive model of VDB is provided. According to the model, talking and muttering-VDB could be treated with atypical antipsychotics, antidepressants, benzodiazepines and anticonvulsants, while the atypical antipsychotic treatment of screaming-VDB would appear to require further investigation.

Acknowledgements

I would like to extend my thanks to the following people:

To Dr. Buck, my supervisor, thank you for your support, guidance and feedback.

To Dr. Janzen and Dr. Cook, thank you for serving on my committee.

To all my family in Newfoundland, thank you for your support and encouragement.

To Jackie, thank you for your encouraging words and for listening to me ramble.

To my co-workers, the staff in clinical records, John, Shauna, Marilynn, and especially to Darlene. Thank you for your support.

Last but not least, to my wife Jodie, thank you for your support and understanding.

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CHAPTER ONE

Introduction

At present in Canada, and indeed in most areas of North America, it is an epidemiological fact that the number of elderly is increasing. Since the likelihood of developing dementia increases as a function of age, it is reasonable to presume that the number of people developing some form of dementia will also increase. In fact, the Alzheimer's Society of Canada estimates that by 2011, there will be 111,560 new cases of dementia per year (The Alzheimer's Society of Canada, 2006) and 215,847 new cases per year by 2031 (Gautrin, Froda, Tetreault, & Gauvreau, 1990). After considering that Canada is presently experiencing a shortage of nurses, physicians and health professionals, and that this shortage is projected to continue for a number of years, it raises the question of what effects the growing dementia population will have on Canada's mental healthcare system.

In order to answer this question and to understand the full impact of our growing dementia population more fully, it is imperative that we be familiar with the current structure of our mental healthcare system. Knowledge of this system will not only allow the reader to understand what happens to a senior citizen when they lose their ability to live independently but it will also illustrate how this change to an individual's circumstance will, in turn, result in effects that ripple throughout the entire country. Nevertheless, the following description should not be considered an inclusive account of all the possible situations and care options that are available to Canada's seniors. Instead, the following description should only be viewed as an outline whose sole purpose is to provide the reader with a simplified version of a very complex process.

In Canada, when an individual can no longer live independently (i.e., due to a personal injury or to an age-related decline in their mental and/or physical functioning) there are several options that the person or their family can consider. For example, an individual can acquire in-home support services whereby a paid caregiver visits their home at set times throughout the day and assists them with their activities of daily living (ADLs). A second option could be for the individual to live with one of their children and if they do not have any children they could consider moving in with a member of their extended family. Finally, if neither of the aforementioned arrangements is suitable or possible, an individual can seek alternative living arrangements within their community.

Once an individual has decided to pursue a community placement, either the person or a family member will have to submit an application to a regional placement coordinator. Upon receiving this application the placement coordinator works with the client and the family member(s) to facilitate the placement process. During this process, topics such as finances, competency, guardianship, choice of facility and most importantly, the status of the client's mental and/or physical functioning are discussed. If the person has few physical and/or mental deficits an "assisted living" facility (i.e., where a paid caregiver prepares the meals and helps the individual with their laundry) might be a good option. Alternatively, for someone who is physically and/or mentally compromised a long-term care (LTC) facility (i.e., a facility where the person can be completely cared for and supervised 24 hours a day) might be more appropriate. In either case, the client (in most situations) is placed in a facility that is best suited to accommodate/manage their needs.

Once a client is placed into a specific facility that person will usually remain there until death, or until their mental and/or physical condition deteriorates beyond the capabilities of that facility. If the client's condition deteriorates, the placement coordinator in consultation with the facility and the client's family/legal guardian will re-evaluated the status of the client's functioning and decide which facility is more appropriate to meet their level of care. With time, as the client continues to deteriorate, he or she will be transferred to other, more appropriate facilities until the person is eventually transferred to a LTC facility. For most, a LTC facility will become their final residence. However, for those who are diagnosed with dementia or for those who develop dementia while living in an LTC facility, the situation is not always this simple (Turner, 2005).

For persons with dementia there is a progressive decline in their mental and physical functioning. As their cognitive impairments become more invasive, the presence of their behavioral and psychological symptoms of dementia (BPSD) becomes more pronounced (American Psychiatric Association, 2000). As the number of these symptoms increases the person with dementia becomes more difficult to manage and such individuals often require more attention and nursing staff to assist with their ADLs (Nordberg, Wimo, Jonsson, Kareholt, Sjolund, Lagergren, et al., 2007). At such a point, most people with dementia would have already been transferred to a LTC facility and since there is no other place for them to live, most LTC facilities have no choice but to seek the guidance of a psychiatrist. If the psychiatrist's recommendations are not beneficial and if the client's behavior continues to be unmanageable, the LTC facility will

usually ask that the client be admitted to a psychiatric institution for further assessment (Turner, 2005).

When a person is admitted to a psychiatric hospital there is an agreement with the LTC facility and the individual's family/legal guardian that the hospital will treat, stabilize the patient's behavior and return them to the facility from which they were admitted. In most cases this is what happens and the mental healthcare system continues to function with the psychiatric hospital being utilized only for the more extreme and/or difficult cases. However, there are certain BPSD that are more resistant to treatment and in many cases, patients that display these symptoms do not return to the LTC facility. Instead, these individuals die in hospital or they remain in hospital until their condition deteriorates and they are once again manageable for a LTC facility (Neville & Byrne, 2007).

As a clinician, I have spent the last 7-years reviewing dementia research and I have experienced first hand the challenge of treating and managing this difficult population. Knowing this, I realize now more than ever that the growing dementia population is going to have a tremendous impact on Canada's mental healthcare system. I also realize that I cannot possibly account for every contingency and consequence that might result from this growing epidemic. However, in order to provide the reader with a sufficient understanding of these growing concerns, I will mention a few of the more obvious consequences.

Research has shown that caring for people either with or without dementia is expensive. However, the cost of caring for a person with dementia is even greater. At present, the annual monetary costs to the country are enormous and considering that our

population is getting older the future projections for healthcare costs are staggering (Sadik & Wilcock, 2003). For example, consider the following scenario. *Imagine that you are a nurse who is trying to get a patient ready for a bath. The water is running and you are walking the client hand in hand to the bathroom. When you enter the bathroom the client becomes restless and starts to yell, "Help, they are trying to drown me". You console the client and assure them that this is not the case, but despite your best reassurances, the client is convinced that you are going to drown them. Three other nurses come to your aid and after 15-minutes you safely get the patient back to their bedroom.* This scenario, and similar situations, comprise the primary reason why people with dementia are more expensive to care for. More nurses and more nursing time equals more money. Furthermore, if the person cannot be managed by an LTC facility, and if the person has to be transferred to a psychiatric hospital, the associated cost of care may increase up to three times that of a LTC facility (Sadik & Wilcock, 2003).

In addition to the cost of caring for people with dementia, it is unlikely that there will be sufficient staff, space or resources to accommodate the increasing population. Accordingly, for people that require placement into the care community there will likely be an extended waitlist and such individuals will have to wait months, possible years before a space becomes available. If this happens, who is going to look after these people? If the person has family, it is likely that one of their children or a member of their extended family will have no choice but to care for their loved one and watch over them while he or she waits for a space to become available. Unfortunately, this is potentially problematic as most people already have busy lifestyles, financial burdens and limited space in their homes. Adding the responsibility of caring for a loved one might make the

home environment incredibly stressful and in some cases lead to elder abuse (see Wang, 2005; Caron, Ducharme, & Griffith, 2006).

For those who are already in the mental healthcare system, residents can expect to be prescribed more sedating medication, to experience an increase in the use of physical restraint (Herrmann, Lanctôt, & Khan, 2004), overcrowding (Caron et al., 2006), and for the reasons just listed an overall decrease in their quality of life (Teresi, Holmes, & Monaco, 1993). Furthermore, as the number of people developing dementia increases it is likely that the number of people that will present with treatment-resistant BPSD will also increase. Considering that such individuals are usually admitted to psychiatric institutions and that most individuals do not leave (Neville & Byrne, 2007) it is likely that the growing dementia population will minimize the access to our psychiatric hospitals and in many cases prevent other Canadians from receiving such specialized interventions.

Having provided a basis for the potential impact of the growing dementia population, what can we do about it? What can be done to prevent the adverse consequences mentioned above? Although there are several answers to these questions researchers have indicated that finding effective interventions for the treatment-resistant BPSD is a global health concern and that as researchers we need to be doing more (Babbage, 2005). Of all the BPSD, one of the most distressing and probably the most resistant to treatment is vocally disruptive behavior (Sloane, Davidson, Buckwalter, Lindsey, Ayers, Lenker, et al., 1997).

After reviewing the available literature on vocally disruptive behavior (VDB), the research suggests that there have been no treatments that have been proven to be effective in all, or even most cases. To date, pharmacological, non-pharmacological and procedural

interventions (i.e., electro-convulsive therapy) have been investigated (see, Kopala & Honer, 1997, Turner, 2005, Snowdon, Meehan, & Halpin, 1994). Most of these studies are single or two participant designs, which amongst other considerations, makes it difficult to generalize these findings to the larger dementia population (Kopala & Honer, 1997). Complicating matters even more is that most research indicates that pharmacotherapy should not be used with this population although such therapy is routinely used in clinical practice. Moreover, when pharmacotherapy is used with this population, it is often done inappropriately (Ballard, O'Brien, Reichelt, & Perry, 2002). Proceeding from this information, the author sought to evaluate the psychotropic treatment of 19 patients with severe dementia that displayed VDB to determine which psychotropic medications, if any, were associated with reductions in the participant's frequency of VDB.

Overview of Thesis

The purpose of this study was to conduct a retrospective review of the interdisciplinary progress notes and medication records of 19 patients with severe dementia and to evaluate which psychotropic medications, if any, were associated with reductions in the patient's frequency of VDB. The intent is to propose a neurological/cognitive model of VDB that integrates the neurotransmitter abnormalities of dementia with neural circuitry of human vocalisation. With this information, clinicians and other health care providers will have a neurological basis for understanding why certain psychotropic medications are beneficial and why others are not. Finally, it is anticipated that the findings of this research will help guide the future treatment of VDB and in doing so enable practitioners to treat the behavior in a more effective manner. If

patients can be treated more effectively, we should see improvements in our patients' quality of life and we should also see our psychiatric hospitals being used more effectively. If our psychiatric hospitals can continue to act, as they were intended I believe that this will help to minimize the impending impact upon our mental healthcare system.

Subsequent Chapters

Chapter two introduces the reader to VDB, its proposed etiology and the use and efficacy of non-pharmacological interventions. Following this review, a summary of the psychotropic medications that have been tried specifically with VDB as well as the recommendations provided by Herrmann & Lanctôt (2007) for the management of the behavioral and psychological symptoms of dementia are provided. Chapter 3 reviews human neurophysiology, the pathology of dementia, research findings on neurotransmitter abnormalities and the neural circuitry of human vocalisation. It concludes by proposing a neurological/cognitive model that integrates the neurotransmitter abnormalities of dementia with the neural circuitry of human vocalisation. Chapter four outlines the methodology and in Chapter five, the results are reviewed. These results are discussed in Chapter six, and implications of the findings are also presented.

Definitions

Vocally disruptive behavior (VDB) is a behavioral and psychological symptom of dementia. It refers to any sound that when uttered is out of the ordinary for a specific situation. Such utterances create inordinate stress on the individual, and may range from

the intermittent repetition of the same word or sound to continual screaming, yelling and/or moaning like behavior.

A **psychotropic medication** is a chemical substance that acts primarily upon the central nervous system (CNS) where it alters brain function, resulting in temporary changes in perception, mood, consciousness and behavior (Kaplan, Sadock, & Grebb, 1994). Typical examples of these medications include citalopram (Celexa®), quetiapine (Seroquel®) and lorazepam (Ativan®).

To date, the scientific and clinical communities have agreed that the **severity of an individual's dementia** can be classified on the basis of their performance on the Mini Mental Status Examination (see Folstein, Folstein and McHugh, 1975; Tombaugh, Kristjansson, McDowell, & Hubley, 1996; Chatfield, Matthews, & Brayne, 2007; Folstein, Folstein, & McHugh, 2007). The Mini Mental Status Examination (MMSE) is a cognitive screening instrument that was developed by Folstein et al. (1975) for the purpose of identifying the nature and severity of cognitive impairment in elderly people with cognitive deficits and psychiatric disturbances. On this instrument, scores of 26 – 30 (30 being the maximum) indicate that the examinee's functioning is intact or that they are experiencing a questionably significant impairment. Scores of 21 – 25 indicate a mild cognitive impairment, 11 – 20 indicates a moderate cognitive impairment and scores of 0 – 10 suggest that the examinee's cognitive functioning is severely impaired (see Pearsall, O'Neill, & Wilcock, 1995).

CHAPTER TWO

LITERATURE REVIEW

Introduction to Vocally Disruptive Behavior (VDB)

Dementia refers to a collection of neuro-degenerative disorders that are characterized by the development of multiple cognitive deficits. These deficits can be the result of the direct physiological effects of a general medical condition, the persisting effects of substance abuse or be of multiple etiologies. As such disorders progress, cognitive impairments become more invasive, functional abilities decline and the BPSD become more problematic and difficult for caregivers to manage (American Psychiatric Association, 2000).

The BPSD are common and serious complications of dementia (Schreinzer, Ballaban, Brannath, Lang, Hilger, Fasching, et al., 2005). They include agitation (CohenMansfield, Werner, & Marx, 1990), aggression (Finkel, 2003), depression (Herrmann & Lanctôt, 2007), psychosis (Haupt, 2000), wandering (Meguro, Meguro, Tanaka, Akanuma, Yamaguchi & Itoh, 2004) and VBD (McMinn & Draper, 2005). These conditions are difficult to manage and many are often resistant to treatment (Schreinzer et al., 2005). They are evident in all types of dementia and their presence varies as a function of the disease's progression (Schreinzer et al., 2005). Of all the BPSD, one of the most distressing and probably the most difficult to treat is VBD (Sloane et al., 1997).

Based on the available literature, the research suggests that screaming (CohenMansfield et al., 1990), wailing (Groulx, 2004), shrieking (Nagaratnam, Patel, & Whelan, 2003), or more generally VDB refers to any sound that when uttered is out of the

ordinary for a specific situation. As a construct, the research has identified four subtypes. These include, screamers (i.e., mostly utter nonsensical noises), talkers (i.e., mostly utter words), mutterers (i.e., mostly utter unintelligible words and syllables of words) and singers (Nagaratnam & Nagaratnam, 2005). As a symptom of dementia, the research suggests that VDB creates a significant amount of stress for the individual and that it threatens the quality of interpersonal relationships with family and caregivers. It would also appear that most individuals exhibiting VDB are inconsolable and that many demonstrate such heightened levels of disruption that they are restricted from communal areas, often spending the majority of their waking hours alone in isolation (Barton, Findlay, & Blake, 2005; Nagaratnam & Nagaratnam, 2005).

Imagine that you are a nurse working in a 75-bed LTC facility and that several of your clients display VDB. Now imagine that one of your clients is repeatedly screaming "ah, ah, ah" while another is counting 1,2,3,4,5 over and over at a volume that can be heard from approximately 30 feet away. You have checked each resident for urinary and fecal incontinence and they are not demonstrating any noticeable indications of pain. You have sat with both residents for 10-minutes, held their hand and softly sung an old-time lullaby. The patient has not responded to your interventions and the surrounding residents are getting agitated. One resident has also started to yell and another person is saying, "If they don't shut her up, I will". You are frustrated. Your level of anxiety has increased and you feel helpless in trying to ease the suffering and discomfort of these troubled individuals. You have no options left. You escort the patients to their bedrooms, put on their favorite music and close the door.

It is situations like the one just described that creates the detrimental impact that was mentioned above. This effect is broad and its influence is experienced by nursing staff, the patient's family, other residents (i.e., if the person lives in an institution) and by the patient themselves. For caregivers and nursing staff the repeated exposure to VDB increases their physiological arousal to such a point that many individual's become susceptible to stress and burnout (Turner, 2005). Their inability to console, comfort or interact with their patient/loved one causes such feelings of helplessness and frustration that many caregivers are forced to "give up" and have no choice but to allow the person to suffer in isolation (Draper, Snowdon, Meares, Turner, Gonski, McMinn, et al., 2000). Please note that the aforementioned situation, although fictitious, is an actual synthesis of clinical experience.

For the other residents, the repeated exposure to VDB is also distressing. It reduces the quality of their daily lives and like for nurses and caregivers, it also increases their physiological levels of arousal. This arousal can manifest itself in many ways and for those who are experiencing dementia there is often an increase in their own demonstration of BPSD (Sloane et al., 1997). Some residents will demonstrate more wandering behavior (i.e., trying to find the resident and help them), while others will become so frustrated with the person's behavior that they will attempt to smother and/or otherwise assault the resident. In other cases, the increased levels of arousal can increase a resident's confusion and in doing so increase their resistiveness to nursing assistance (Sloane et al., 1997).

Like other residents, their caregivers and their family members, people who are vocally disruptive also experience a number of adverse effects from their behavior. Such

individuals generally have a poor quality of life. They are restricted from communal areas and in many cases they receive minimal group and/or individual interaction (Sloane et al., 1997). Physiologically, they are in a constant state of arousal and their repetitive vocalizing can cause sore throat, hoarseness and stress to their abdominal muscle. In addition, there is no consensus about how to treat VDB. Nevertheless, even without such guidelines the research suggests that persons with VDB are often heavily medicated and placed at risk for adverse drug reactions (Ballard et al., 2002). To make matters worse, when the adverse effects to nursing staff and are combined with the deleterious effects on other residents, many clients are discharged from their LTC facilities and admitted to psychiatric hospitals for further treatment (Sloane et al., 1997).

The research suggests that the BPSD are common and serious complications of dementia and that such symptoms are evident in all types of the illness (Schreinzer et al., 2005). In fact, Herrmann & Lanctôt (2007) suggest that at some point during their illness all persons diagnosed with dementia will exhibit at least one BPSD. In light of such information, it appears that there is some consensus about the prevalence of the BPSD, especially as it pertains to physical aggression, hallucinations, delusions, agitation, and wandering. However, after conducting a systematic review, it was readily apparent that the same could not be said for VDB and that across most epidemiological studies the prevalence rates of VDB have varied from 11 to 85 percent in institutionalized settings (Burgio, Scilley, Hardin, & Hsu, 2001). In this regard, it appears that part of the reason for this variation is that in most cases VDB has been defined under the broader term of agitation and not as an individual BPSD. For example, CohenMansfield & Billig (1986) defined agitation as "inappropriate verbal or motor activity that is not an obvious

expression of need or confusion" (p.712) and later classified agitation into three manifestations (CohenMansfield et al., 1990). These included: physically aggressive behavior (i.e., hitting, kicking and cursing); physically non-aggressive behavior (i.e., restlessness, pacing, inappropriate robing and disrobing); and verbally agitated behavior (i.e., complaining, negativism and repetitious phrases) (CohenMansfield et al., 1990). In this fashion, it is often difficult to determine which type of agitation these studies are measuring and if in fact VDB (as it is defined above) is present in the targeted sample. To that end, Burgio et al. (2001) have indicated that once VDB is differentiated from other forms of agitation, prevalence rates are routinely reported from 11 to 30 percent for most community and institutionalized settings.

As with other BPSD, VDB is assumed to have multiple etiologies (Meares & Draper, 1999) and although there is some debate, most research suggests that contributors are endogenous and/or exogenous. Studies indicate that severity of cognitive impairment (Nagaratnam et al., 2003), inability to perform activities of daily living (CohenMansfield & Werner, 1997), depression (Dwyer & Byrne, 2000), pain (Manfredi, Breuer, Meier, & Libow, 2003) and an inability to communicate (Matteau, Landreville, Laplante, & Laplante, 2003) are probable causes of VDB. Other associations include psychosis (Finkel, 2003), gout (Liu, Raji, Twersky, & Riggs, 2000), inability to cope with stress (Ragneskog, Gerdner, Josefsson, & Kihlgren, 1998), environmental factors (Groulx, 2004), the behavior of caregivers (Babbage, 2005), constipation (Kopala & Honer, 1997) and delirium (Johnson, 1990). Finally, the research suggests that VDB is not unique to one type of dementia and that each type is equally as likely to demonstrate the behavior (Meares & Draper, 1999). In fact, in a study by CohenMansfield, Werner,

Hammerschmidt, & Newman (2003) the only difference between the type of dementia diagnosis and VDB was that individuals with Dementia of the Alzheimer's Type (AD) sounded longer utterances than individuals with Vascular Dementia (VaD).

The available research suggests that VDB is difficult to treat and that in most cases interventions have limited success (McMinn & Draper, 2005). Apparently, part of the reason for this failure is that clinicians and care-providers are not systematically evaluating the possible causes of a person's behavior. Before any interventions (i.e., pharmacological, non-pharmacological or procedural) are attempted, clinicians and care-providers should attempt to ascertain what is the underlying cause to the person's behavior (McMinn & Draper, 2005). For example, is the VDB related to over-stimulation or not enough stimulation? Is the person constipated, dehydrated, in pain or is their behavior an attempt to communicate a specific need? Only when these questions have been answered should a clinician decide to pursue more conventional types of treatment (Sloane et al., 1997).

Deciding how to treat VDB is difficult. Even when all possible underlying causes have been eliminated and the behavior is best explained by some neuro-pathological change (i.e., atrophy or degeneration of neural pathways to the frontal lobe) it is still difficult to determine which type of intervention is best to use (Kopala & Honer, 1997). Most research suggests that non-pharmacological interventions or behavioral therapy should be used (see Turner, 2005), while other research (see Snowdon et al., 1994) suggests that such interventions are not effective and that with caregivers in such a short supply there is often no time to administer such interventions. Having said that, there is empirical support for non-pharmacological interventions and to date, bright light therapy

(Thorpe, Middleton, Russell, & Stewart, 2000), calming music (Remington, 2002) snoezelen therapy (van Wèert, van Dulmen, Spreeuwenberg, Ribbe, & Bensing, 2005) and behavior modification (Buchanan & Fisher, 2002) have been investigated. Other interventions have included glider swings (Snyder, Tseng, Brandt, Croghan, Hanson, Constantine, et al., 2001), environmental modifications (Turner, 2005), sensory stimulation (Burns, Byrne, Ballard, & Holmes, 2002), aromatherapy (Ballard et al., 2002), false present therapy (Peak & Cheston, 2002), and staff education (Turner, 2005).

Although there is some evidence to support the use of non-pharmacological interventions the research indicates that most interventions are only beneficial with people who experience mild and moderate dementia. For individuals with severe dementia non-pharmacological interventions have minimal effect and in most cases do little to reduce the intensity and/or frequency of their vocal disruption. To that end, the mainstay for treating VDB has been pharmacotherapy. In extreme cases electro-convulsive therapy (ECT) has been used, but as a rule most alternative decision-makers prefer the use of pharmacotherapy (Snowdon et al., 1994).

Introduction to Pharmacotherapy

Before discussing the available literature, it should be understood that much of the research on BPSD does not address specific behavioral disturbances. Instead, the research has focused on the broader term of agitation and investigated clusters of BPSD as opposed to individual behaviors (Robert & Allain, 2001). Studies of this design, although valuable, limit our ability to examine the differential effects of pharmacotherapy. In consequence, it is not possible to determine which interventions are the most effective for specific types of behaviors (Herrmann, 2001). If we are going to determine which

medications are the most effective for specific BPSD (i.e., VDB) future research will need to change its focus and start to evaluate each BPSD as an individual symptom as opposed to a cluster of behavioral disturbances. With this in mind, some historical concerns about the treatment of dementia as well as the general process for determining the use of psychotropic medications will be introduced. Following this introduction, the available research on the psychotropic treatment of VDB will be discussed as well as the recommendations provided by Herrmann & Lanctôt (2007) for the management of the BPSD.

By the 1980s there was a growing concern that psychotropic medications were being overused, misused and administered by individuals who were unaware of their expected benefits or potential adverse effects. In the United States, these concerns prompted the passing of the Omnibus Budget Reconciliation Act (OBRA) in 1987, which among other things restricted the use of psychotropic medications in institutionalized settings. The Act further mandated that all patients receiving these medications receive low doses and that they be closely monitored for drug effectiveness and adverse effects (Frenchman, 2000). Since then, the treatment approaches used in institutionalized settings have changed. In present practice there is less reliance on medication and more use of psychosocial and behavioral interventions (see Frenchman, 2000 & Herrmann, 2001). However, it is also important to note that despite the growing acceptance and utilization of non-pharmacological interventions, psychotropic drug therapy continues to prevail (Levy, Burgio, Sweet, & Bonino, 1994).

Although the use of pharmacotherapy has remained prevalent, research suggests (see Herrmann, 2001, Hermann & Lanctôt, 2007) that the current treatment of dementia

is not necessarily guided by evidenced-based support from clinical trials. Instead, it appears that the BPSD are treated by a "rational" approach whereby each client is treated according to their symptom's association to a specific psychiatric illness or medical condition. For example, Yudofsky et al (see Herrmann, 2001) have recommended the use of antipsychotics for BPSD associated with psychosis, carbamazepine for aggression associated with seizures, lithium for aggression associated with mood disorder and beta-blockers for chronic aggression. Although these approaches may initially appear reasonable there is insufficient evidence to support their use, and most researchers suggest that these therapies cannot be recommended as the standard for treating people with dementia. However, some findings recommend that the treatment of dementia should be multifaceted and that each patient should be assessed from a medical, environmental and behavioral perspective (Herrmann, 2001).

Medically, treating a patient with dementia must include a physical examination, psychological assessment, and laboratory investigations to rule out concomitant medical illness such as a urinary tract infection. The patient's type of dementia must be accurately diagnosed and the clinician should ensure that all existing medical concerns (e.g., arthritis, chronic pain and congestive heart failure) are properly treated. Furthermore, the clinician should also obtain a detailed medical/family history and be fully aware of all current medications (i.e., prescription, non-prescription, vitamins, minerals and complementary and alternative medicines).

When assessing a patient from an environmental perspective the physician should consider both the environment in which the patient lives and the type of BPSD that the client is displaying. If a patient is impulsive, disoriented to space and is still living at

home, the clinician will have to consider the patient's risk for personal injury and their likelihood of wandering away from home. In such situations, a live-in caregiver or an electronic monitoring device (e.g., wander guard) might be recommended before considering pharmacotherapy. On the other hand, if the patient is institutionalized and displays wandering or vocally disruptive behavior, the clinician will have to consider the patient's potential for falling and their potential of harm from other residents whom they disturb (Herrmann, 2001). For example, if the clinician were to prescribe an antipsychotic, it might reduce the patient's risk of being harmed by another co-resident (i.e., the patient would be less disruptive secondary to sedation), but at the same time this intervention could increase the patient's risk for falling. In situations like this, the physician should consider another type of psychotropic medication such as an antidepressant or at the very least attempt to use a series of non-pharmacological interventions before commencing pharmacotherapy. If the non-pharmacological intervention(s) and the alternative pharmacotherapy are ineffective, the clinician might have to reconsider the antipsychotic medication and start the medication with special precautions in place. Such precautions might include a pro re nata (PRN) prescription of benzotropine (Cogentin®), which could be used as needed to offset any adverse effects to the patient's cognition or gait (Herrmann, 2001).

Once the physician has conducted a thorough medical assessment and assessed the patient's environment, the physician will have to ensure that the targeted BPSD has been clearly identified and that strategies have been developed to assess its nature, intensity and frequency. Such strategies might include having a nurse or a suitable care provider complete a daily behavior tracking form or behavior-rating scale at set times

throughout the day. Using this approach a clinician should be able to determine when the behavior is the most frequent (i.e., morning, afternoon or within 10-minutes after having a bath) and in some cases determine why the behavior is occurring. Furthermore, if the initial non-pharmacological interventions are unsuccessful and if pharmacotherapy is necessary, a clinician can use the information from the behavioral assessment and determine what time of the day it is best to prescribe a specific medication.

Once a clinician has exhausted all other treatment interventions (i.e., non-pharmacological, behavioral and environmental) there are several factors that he or she will need to consider before starting pharmacotherapy. First, the clinician will have to decide what is the most likely cause of the patient's behavior and as mentioned above treat the behavior based on its association to other psychiatric illnesses or medical conditions. Second, the clinician will also have to consider the numerous age-related changes (i.e., reduced renal, cardiovascular and liver function) that can affect the metabolism of certain medications, and thus choose a medication or dose that is the most appropriate for the specific client. Some psychotropics might interfere with the patient's current medications or they might worsen an existing medical condition. For example, if a patient were being treated with carbamazepine for a seizure disorder the use of olanzapine (Zyprexa®) for aggression related to psychosis would not be recommended. Carabamazepine can induce the hepatic metabolism of olanzapine and result in a 50% increase in its total body clearance. If the patient was prescribed olanzapine, they would in effect need a higher dose of the drug to produce the desired clinical effect and in doing so the higher dosage could increase the patient's potential for developing adverse effects (Pagliaro & Pagliaro, 1998). Furthermore, clinicians also have to be concerned about the

potential anticholinergic effects of antipsychotics and certain types of antidepressants. Such effects can worsen a patient's confusion, precipitate a delirium and in some cases reverse the effects of cholinesterase inhibitors (Herrmann, 2001).

Based on the information noted previously, each patient should be treated on a case-by-case basis and if necessary, pharmacotherapy should be started with the lowest possible dose. Providing that the client does not have an adverse drug reaction, the dose of medication should be increased slowly until the patient demonstrates a favorable response (i.e., as determined by the clinician) or until an adverse effect warrants decreasing or discontinuing the medication. Patients should also be monitored for medication effectiveness, excessive sedation and adverse effects to their cognition and gait. Finally, once the patient has shown a favorable response for a specific period of time (as determined by the clinician), the physician should make every effort to reduce the dose and if possible to discontinue the medication completely (Herrmann, 2001).

In summary, treating a person with dementia should be multifaceted and it must include a medical, environmental and behavioral assessment. Once a person has been assessed the research indicates that the first-line interventions should be non-pharmacological and that if pharmacotherapy is necessary it should be started at the lowest possible dose. Furthermore, once the patient has shown a favorable response for a specific period of time the physician should make every effort to reduce the dose and if possible to discontinue the medication completely. Finally, whenever considering the use of a psychotropic medication the choice of medication should always be based on the agent's pharmacological characteristics and how those characteristics will effect a

patient's existing medical condition(s) and/or interact with their concomitant medications.

Psychotropic Medications Used to Treat VDB

There have been numerous publications to support the use and effectiveness of pharmacotherapy in the treatment of the BPSD. However, after conducting a systematic review of the available literature the same could not be said for the patients that display VDB, although Nagaratnam & Nagaratnam (2005) have suggested that antidepressants, anticonvulsants, antipsychotics and cholinesterase inhibitors are commonly prescribed. As such, a detailed search of the interdisciplinary literature using Medline, Embase, PsychoInfo, Scirus, AARG Ageline and Academic Search Premier databases was conducted. Using the keywords: dementia, noise, screaming, disruptive vocalisation and pharmacotherapy the author found five publications that specifically investigated VDB (please see Table 1 below). In the following review, these articles will be discussed as well as the recommendations provided by Herrmann & Lanctôt (2007).

Antidepressants

A number of case reports, series and uncontrolled trials suggest that antidepressant pharmacotherapy is effective for treating VDB (see Greenwald, Marin, & Silverman, 1986; Ramadan, Naughton, & Bassanelli, 2000; Kim, Bader, & Jones, 2000). In Greenwald et al. (1986) the authors described the case of an 82-year old woman with AD that presented with screaming and head-banging behavior. Previous trials of thiothixene, haloperidol, oxazepam and tranlcypromine were unsuccessful and the patient experienced significant adverse effects. The patient was started on trazodone (Desyrel®) and over a three-week period her dose was increased to 150mg twice daily. Within three

weeks, her head banging had decreased, her mood improved and her screaming was no longer constant. Following another three weeks at this dosage, adjunctive therapy with 1g of the serotonin (5-HT) precursor L-tryptophan was started. After another two weeks and reducing her dose of trazodone to 100mg twice daily and increasing her L-tryptophan to 2.5 g the patient's screaming and head banging had almost stopped completely.

Trazodone is a triazolopyridine antidepressant that produces its antidepressant effect by blocking 5-HT_{2A} and 5-HT_{2C} receptors. In addition, research by Luparini, Garrone, Pazzagli, Pinza, & Pepeu (2004) suggests that trazodone's therapeutic effect may also be obtained through its ability to reduce gamma-aminobutyric acid (GABA) ergic tone in the CNS as well as by its α – adrenergic antagonism (see Kozman, Wattis, & Curran, 2006). Through the blockade of 5-HT_{2A} receptors trazodone is able to decrease extracellular levels of GABA and thereby increase the levels of 5-HT. With 5-HT more available, neuronal functioning can improve and the improvements in neural functioning can result in improved serotonergic neurotransmission (Delgado, 2004).

According to Herrmann & Lanctôt (2007), antidepressants such as trazodone have been used for the treatment of agitation, aggression, depression and sleep disturbances. Unfortunately, there are few randomized controlled studies that allow us to make definitive conclusions about its role as a treatment for BPSD. Of the available results, trazodone has been shown to be more effective than buspirone and just as effective as haloperidol for reducing agitation. Furthermore, when compared to haloperidol, trazodone was better tolerated and it resulted in fewer adverse effects and dose reductions. Accordingly, and based on the available research, trazodone use is supported in the treatment of the BPSD, however based on the absence of randomized controlled

Table 1: Summary of empirical findings of pharmacotherapy used to treat vocally disruptive behavior

References	Medication & Dosage	Treatment Outcome	Sample Size, MMSE & Diagnosis
Greenwald et al., 1986	Trazadone (Desyrel®) 200 mg daily & L-tryptophan 2.5 g daily	Screaming and echolalia almost completely stopped following treatment	N = 1, Diagnosis: AD
Kim et al., 2000	Citalopram (Celexa®) 40 mg daily	Significant reduction in verbal agitation	N = 2 MMSE = 0 Diagnosis: AD
Kopala & Honer, 1997	Risperidone (Risperdal ®) 1.5 mg daily	Vocalisations decreased to less than 20% of baseline	N = 2, MMSE = 9/30 Diagnosis: Mixed &VaD
Rosin, Levine, & Peskind, 2001	7 mg – 14 mg transdermal nicotine	1) Verbal agitation estimated to be 95% reduced 2) Dramatic decrease in vocalizations	N = 2 Diagnosis: AD & VaD
Ramadan, et al., 2000	Paroxetine (Paxil ®) 40 mg daily	94 % reduction in agitation on the CMAI at 3-months. Overall clinically significant reduction in verbal agitation	N = 15 MMSE = < 10/30 Diagnosis: AD, VaD & Mixed

Abbreviations & Considerations:

- CMAI (CohenMansfield-Mansfield Agitation Inventory)
- MMSE (Mini-Mental Status Exam)
- AD (Dementia of the Alzheimer's Type)
- VaD (Vascular Dementia)
- Mixed (Dementia of Multiple Etiologies - Diagnosed with AD & VaD)
- ** Medications are listed as total daily dose at the end of the study
- *** MMSE score presented where available

trials (RCTs) the use of trazodone cannot be recommended as a treatment for the BPSD (Herrmann & Lanctôt, 2007).

Besides trazodone, both citalopram (Celexa®) and paroxetine (Paxil®) have been shown to be effective for reducing the frequency and intensity of VDB in some persons with dementia (see Ramadan et al., 2000; Kim et al., 2000). Collectively, these medications and others like them refer to a newer class of antidepressant called the selective serotonin reuptake inhibitors (SSRIs). Medications in this group are generally well tolerated in the elderly (Ramadan et al., 2000) and some have suggested that they are more effective than their predecessors (i.e., tricyclic antidepressants (TCAs) and the monoamine oxidize inhibitors) for alleviating depression (Leinonen, Skarstein, Behnke, Agren, Helsdingen, & Nordic Antidepressant Study Group, 1999; Ramadan et al., 2000). Each SSRI varies slightly in their pharmacological profile, but in essence each medication produces its antidepressant effect in the same way. The effect is produced by increasing the availability of serotonin (5-HT) through the indirect down-regulation of 5-HT_{1A} autoreceptors. Activation of these autoreceptors prevents the pre-synaptic cell from re-absorbing synaptic 5-HT and in doing so it increases 5-HT's synaptic availability. The resulting activation creates a feedback inhibition in the raphe nucleus and in conjunction with autoreceptor activation increases serotonergic neurotransmission (BezchlibnykButler, Aleksic, & Kennedy, 2000).

Ramadan et al. (2000) conducted an open label trial with 15 patients that demonstrated VDB. There were 12 females and 3 males who were diagnosed with AD, VaD or a mixture or the two. The total mean score for all participants on the MMSE was 9.2 (SD = 4.5) and 53 percent were classified as being severely demented. Patients'

vocalisations were measured with the CohenMansfield Agitation Inventory (CMAI) at baseline (i.e., one month before commencing paroxetine) and every two weeks thereafter for three months. Patients were started on 10mg of paroxetine and the dosage was increased every two weeks by 10 mg if the participant's score on item 23 or 29 of the CMAI was four or greater. The maximum total daily dose was 40mg and the patients did not receive any neuroleptic medications during the study. In summary, the authors indicated that the use of paroxetine appeared to benefit 13 of the 15 participants. There were minimal adverse effects and overall the intervention was well tolerated.

In a similar study, Kim et al. (2000) described the cases of two males with AD that demonstrated incessant uttering of nonsensical words and verbal agitation. One gentleman scored 5 on the MMSE and the other scored 0. Previous attempts to treat the verbal behavior with valproic acid, propranolol, clonazepam, lorazepam, oxazepam, risperidone, olanzapine and lithium were unsuccessful. In both cases the patient was started on 20mg of citalopram and increased to a total daily dose of 40mg. Each participant showed considerable reductions in their verbal agitation (as indicated by the authors). There were no adverse effects and both patients were described as having responded well to the intervention. In fact, one patient's citalopram had to be discontinued (because he developed trouble swallowing) and within 5-days of discontinuing the dose the patient's behavior returned to its previous levels.

According to Herrmann & Lanctôt (2007), antidepressants such as the SSRIs have been used for the treatment of agitation, aggression and depression. Unfortunately, there are few randomized controlled studies that allow us to make definitive conclusions about their role as a treatment for the BPSD. In dementia, the SSRIs have been recommended

as a treatment for depression, but due to the limited number of RCTs, more research is needed before they can be recommend as a treatment for other BPSD (Herrmann & Lanctôt, 2007).

Antipsychotics

The antipsychotic medications refer to a group of chemical compounds that are indicated for the management of the manifestations of schizophrenia and related psychotic disorders. They are divided into two classes, the typical and atypical antipsychotics. The typical antipsychotics include medications such as haloperidol (Haldol®), methotrimeprazine (Nozinan®) and chlorpromazine (Largactil®) that produce their therapeutic effect by demonstrating high affinity and high occupancy of D_2 receptors (CPS, 2006). They are efficacious for treating the BPSD, but their tendency to cause adverse effects raises questions about their use. For example, after reviewing 17 RCTs of typical antipsychotics in the treatment of dementia, response rates were found to be significantly higher than placebo, but were matched by the rates of adverse effects. The most common adverse effects are sedation, falls, dizziness, and confusion, while more serious effects (i.e., neuroleptic malignant syndrome & tardive dyskinesia) can also occur (Herrmann & Lanctôt, 2007).

After reviewing the available literature it is clear that the mainstay for treating the BPSD has been the use of atypical antipsychotics (Herrmann & Lanctôt, 2007). Unlike typical antipsychotics, the atypicals are generally better tolerated in the elderly and they do not produce as many and/or as frequent adverse effects. However, like all medications there is still the potential for adverse effects. For example, in 2005 Health Canada released a warning that based on RCT data, all antipsychotic medications appeared to be

associated with increased mortality in persons with dementia and that considering this information they could not support atypical antipsychotic medications as a treatment for the BPSD. Despite this warning, atypical antipsychotics are still routinely prescribed and they continue to be one of the most efficacious agents for treating the BPSD (Herrmann & Lanctôt, 2007).

Atypical antipsychotic treatment of the BPSD has included risperidone (Risperdal®), olanzapine (Zyprexa®), quetiapine (Seroquel®), aripiprazole (Abilify®), and clozapine (Clozaril®), although there is limited support for the use of aripiprazole or clozapine. In addition, both aripiprazole and clozapine may cause potentially lethal effects in the elderly, and due to the need for routine blood monitoring clozapine is usually administered in a hospital setting (Kozman et al., 2006; Herrmann & Lanctôt, 2007). As such, the current research suggests that risperidone, olanzapine, or quetiapine should be considered as the first line antipsychotic pharmacotherapy before trying other atypical antipsychotics and certainly before using a typical antipsychotic. The question that remains is of these interventions, which medication should be used for a specific BPSD (Herrmann & Lanctôt, 2007)?

Based on the available research, risperidone appears to be more efficacious than olanzapine (Frenchman, 2000, Frenchman, 2005) and quetiapine (Herrmann & Lanctôt, 2007) as a treatment for the BPSD. It is better tolerated than olanzapine and adverse effects such as unsteadiness, falls, constipation, and sedation are observed less frequently (Frenchman, 2000). Thus, risperidone has been suggested to be the preferential choice for antipsychotic pharmacotherapy, although clinicians still have to be conscientious when prescribing this medication, as risperidone use can also cause adverse effects.

Furthermore, when a patient is sensitive to neuroleptic medication or if a person is diagnosed with Dementia with Lewy Bodies (DLB) or Parkinson's Disease Dementia (PDD), the research suggests that risperidone and olanzapine should be avoided and that if antipsychotic pharmacotherapy is necessary quetiapine should be implemented (Tariot & Ismail, 2002).

To date there has been only one study that has specifically investigated antipsychotic pharmacotherapy as a treatment option for VDB. In this study, Kopala & Honer (1997) summarized the treatment of two women with severe dementia who after a cerebral vascular accident displayed persistent high-pitched screaming. Both patients scored 9 out of 30 on the MMSE and all laboratory investigations were within their normal limits. One patient was diagnosed with mixed dementia and the other with multi-infarct dementia. After unsuccessful attempts with haloperidol, methotrimeprazine, chlorpromazine, loxapine, clonazepam, chloral hydrate, phenytoin and lorazepam all antipsychotic medications were decreased and subsequently discontinued. Both patients were then given a three-week washout period and started on risperidone 0.5mg twice daily. The total daily dosage of risperidone was increased to 1.5mg (i.e., 0.5mg A.M. and 1mg at bedtime) and within three weeks both patients were noted to have a 80 to 90 percent improvement over the baseline assessment in the frequency and intensity of their screaming behavior.

Risperidone is an atypical antipsychotic that like most antipsychotics is indicated for the management of schizophrenia and related psychotic disorders (CPS, 2006). It is well tolerated in the elderly (but adverse effects do occur) and it has proven to be efficacious for treating psychosis, aggression, agitation and sleep disturbances (Herrmann

& Lanctôt, 2007). Pharmacologically, risperidone binds with high affinity to 5-HT_{2A}, D_2, and α_1-adrenergric receptors. It also binds, albeit with lower affinity to α_2-adrenergic and histamine (H_1) receptors. Risperidone has no affinity for D_1 or muscarinic cholinergic (M) receptors (CPS, 2006). Unlike risperidone, olanzapine displays high affinity for numerous receptors. These include D_1, D_2, D_3, D_4, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_6, $M_1 - M_5$, H_1, and α_1-adrenergic. However, like risperidone olanzapine also demonstrates higher occupancy of 5-HT_{2A} receptors than it does for D_2 receptors. Like olanzapine and risperidone, quetiapine also demonstrates the same selectivity for 5-HT_2 receptors, although unlike olanzapine its receptor affinity is limited to 5-HT_2, 5-HT_{1A}, D_1, D_2, H_1, and α_1-adrenergic receptors. Furthermore, quetiapine has low affinity for α_2-adrenergic receptors and no affinity for the M or benzodiazepine receptors (CPS, 2006).

Anticonvulsants

Although anticonvulsants have not been studied specifically with VDB there is considerable research on their use as a treatment for the BPSD. To date, carbamazepine (Tegrotol®), lamotrigine (Lamictal®), gabapentin (Neurotonin®), valproic acid (Depkene®), and topiramate (Topamax®) have been investigated. Of these medications, carbamazepine (CBZ) has been the most studied and at present it represents one of the most efficacious medications for treating the BPSD. Despite this evidence, drug-drug interactions and intolerance in the elderly limit its use and many clinicians resort to newer anticonvulsants, whose pharmacologic profiles are more favorable in the elderly (Herrmann & Lanctôt, 2007).

CBZ is an iminodiabenzyl medication that has been approved by the Food and Drug Administration (U.S.A.) for the treatment of temporal lobe epilepsy and trigeminal

neuralgia (Kaplan et. al., 1994). Pharmacologically, CBZ reduces L-type calcium channel activation by depolarization, and may block the excitatory neurotransmitter glutamate at N-methyl-D-aspartate (NMDA)-type receptors (Kozman et al., 2006). In terms of managing the BPSD, CBZ reduces agitation and aggression and has been shown to produce emotional stability (Herrmann & Lanctôt, 2007). For example, using a randomized, placebo-controlled design, Olin, Fox, Pawluczyk, Taggart, & Schneider (2001) demonstrated that CBZ has modest effects in reducing agitation in individuals who were treatment resistant to antipsychotic medication. In this study the participants included 16 individuals (aged 63-86 years) whose mean MMSE score at baseline was 6.0 (SD = 3.6). Individuals were recruited from the Pharmacology Program of the USC Alzheimer's Disease research program. Following a 6-week, double blind, placebo controlled, parallel group design the authors used Mann-Whitney *U* tests to compare the mean change between the two treatment groups. Collectively, the results demonstrated a significant main effect in the direction of improvement on the Brief Psychiatric Rating Scale (BPRS), indicating that CBZ has modest effect in treating participants who had previously not responded to antipsychotic medications. Others findings (see Tariot, Erb, Podgorski, Cox, Patel, Jakimovich, et al., 1998; Lemke, 1995) have also supported the use of CBZ as a treatment for the BPSD, but for reasons already stated, most clinicians prefer the use of the newer anticonvulsants.

To date, gabapentin, topiramate, lamotrigine, and valproic acid have been investigated, but only valproic acid has been studied in a RCT. According to Herrmann & Lanctôt (2007) five RCTs have been completed and all have revealed negative results on the primary outcome, although some positive outcomes have been reported on secondary

measures. Overall, valproic acid was found to be ineffective at lower doses, while at higher doses it produced too many adverse effects. For the other anticonvulsants, some support for their use has been revealed through case studies, case reports and small sample studies, but like most research on the treatment of the BPSD none have been investigated using a RCT. The literature suggests that even though these medications are routinely used in clinical practice there is insufficient support to recommend their use in the treatment of the BPSD (Herrmann & Lanctôt, 2007).

In terms of pharmacology, gabapentin is structurally related to GABA, but the precise mode of action is yet to be discovered. Research indicates that it does not interfere with the metabolism of GABA, its inhibition, uptake or degradation. Instead it is likely that gabapentin works by interfering with calcium channels and arguably by altering neurotransmitter release (CPS, 2006; Kozman et al., 2006). Other anticonvulsants (i.e., valproic acid) are thought to enhance the function of GABA as well as CNS serotonin, while topiramate, in addition to enhancing GABAergic function, has been shown to antagonize subtypes of the glutamate receptor (CPS, 2006).

Benzodiazepines

It appears that there are no relevant studies of the benzodiazepines, buspirone or beta-blockers as a treatment for VDB. There were however, several studies that investigated the efficacy of these medications as an intervention for the BPSD. For the benzodiazepines, the available research suggests that although these agents are effective for reducing agitation, their potential for developing dependence, as well as the risk for causing adverse effects limits their use to short-term or PRN (Herrmann & Lanctôt, 2007). Furthermore, the literature suggests that for persons with dementia short-acting

benzodiazepines such as lorazepam or oxazepam should be considered first, even though longer acting agents, such as clonazepam have also been demonstrated to be helpful (Hermann, 2001).

Benzodiazepines are classified as anticonvulsants, anxiolytics, sedatives, and hypnotics. Depending on the agent that is chosen, benzodiazepines can be used to treat anxiety disorders, panic disorder, insomnia, seizure disorders, alcohol withdrawal, skeletal muscle spasticity and they can also be prescribed as a perioperative medication. In terms of pharmacology, the benzodiazepines primary mode of action is believed to result from its affinity for the $GABA_A$ receptor. Through this mechanism, benzodiazepines enhance GABAergic function and increase CNS inhibition. The associated inhibition creates a generalized feeling of calmness that is typically observed as reduced agitation and/or anxiety in those that are diagnosed with anxiety disorders (CPS, 2006).

Beta Blockers

Pharmacologically, beta-blockers such as propranolol (Inderal®) and pindolol (Visken®) exert their therapeutic effect by nonselective antagonism of β_1 and β_2 adrenergic receptors. They are used for the treatment of hypertension and as a prophylactic agent for angina pectoris. Propranolol has also been used for prophylaxis of migraine headaches (CPS, 2006) and pindolol has been used as an adjunct to pharmacotherapy with SSRIs (BezchlibnykButler, Jeffries, & Virani, 2007). In terms of adverse effects, the beta-blockers can produce nausea, diarrhea, orthostatic hypotension, hallucinations, insomnia, dizziness, and bradycardia (CPS, 2006).

To date, both propranolol and pindolol have been supported as a treatment for aggression and agitation in persons with dementia. However, like most pharmacological interventions more research is needed before these psychotropics can be recommended as a treatment for the BPSD (see Peskind, Tsuang, Bonner, Pascualy, Riekse, Snowden, et al., 2005; Herrmann, Lanctôt, Eryavec, & Khan, 2004). Although, the research has demonstrated some success for the beta-blockers and it would appear that pindolol has been beneficial for treating verbally aggressive behavior. For example, in a recent study by Herrmann, Lanctôt, Eryavec, & Khan (2004) the authors demonstrated that pindolol was associated with reduced verbal aggression in 11 out of the 16 patients with AD. Unfortunately, the authors did not specify whether uttering threats and cursing (i.e., as measured by the Overt Aggression Scale) had been reduced or if in fact it was VDB. Based on these results, the research has not indicated whether or not the beta-blockers are effective for treating VDB, but after considering VDB is routinely classified within the broader term of agitation it is likely that for some people, the beta-blockers would be an effective intervention.

Buspirone

Buspirone is a nonbenzodiazepine anxiolytic that exerts its therapeutic effect blocking 5-HT_{1A} receptors as well as nonselective interaction with D_2 receptors (CPS, 2006). It is generally well tolerated in the elderly and it has an adverse effect profile that is similar to placebo (Herrmann & Lanctôt, 2007). In regards to the BPSD, buspirone has been reported in several uncontrolled trials to be useful for treating the agitation associated with dementia (Herrmann, 2001). For example, in a study by Hermann & Eryavec (1993) the authors evaluated the effect of buspirone on 16 patients with

dementia, average age was 78.1 years (SD = 7.9). Of the 16 participants, 7 participants had AD, 6 had VaD and 3 were alcohol-induced dementia. Their MMSE score at baseline was 11.3. Buspirone was started at 5mg twice daily and was increased based on the medication's efficacy and how well the drug was tolerated. Treatment ranged from 4-days to 12-months and the treatment's effect was measured with the Clinical Global Impression Scale. At the end of the study, 6 of the 16 participants were rated as much improved to very much improved, while the other participants were rated as minimally improved to very much worse. Collectively, the authors held that buspirone holds promise as a modestly effective and relatively safe alternative to neuroleptics in the treatment of agitation and other BPSD. In a later study, Levy et al. (1994) also demonstrated that buspirone was effective for treating agitation in persons with AD and suggested that patients appeared to respond best to doses of 30mg a day or higher. Collectively, the research on the effectiveness of buspirone as a treatment for the BPSD is inconclusive and to complicate matters further the available data indicates that the number of people who respond to buspirone is equivalent to those that do not. Based on these results, there is insufficient evidence to support buspirone's use in the treatment of dementia, but like most psychotropic interventions more research is needed (Herrmann & Lanctôt, 2007).

Cognitive Enhancers

After reviewing the available literature, the research suggests that anti-dementia drugs are efficacious for slowing the dementing process and that for many individuals these agents will temporarily improve their cognitive abilities and behavioral presentation (Kozman et al., 2006). In Canada, the currently approved cognitive enhancers for the

treatment of AD are donepezil (Aricept®), galantamine (Reminyl®), rivastigmine (Exelon®), and the NMDA antagonist memantine (Ebixa®) (Herrmann & Lanctôt, 2007). Collectively, donepezil, galantamine, and rivastigmine are referred to as the cholinesterase inhibitors (ChEIs) whose primary mode of action is inhibiting the function of two cholinergic enzymes, acetylcholinesterase (AChE) and butyrlcholinesterase (BuChE) (Rivas-Vasquez, 2001).

Donepezil's pharmacologic profile indicates that it is selective for AChE but has negligible effects on BuChE. It is well tolerated in the elderly and its most common adverse effects are cholinergic in nature (i.e., nausea, diarrhea and vomiting). Rivastigmine also inhibits AChE, but unlike donepezil, rivastigmine is selective from brain areas that are important for cognition and memory. In addition, rivastigmine also inhibits the effects of BuChE, which as noted below becomes more evident as the disease progresses. Of all the ChEIs, rivastigmine produces the most robust cognitive effect and based on this ability, some have proposed that its pharmacological profile might represent a theoretical advantage for treating patients that are more severely demented.

Unlike rivastigmine, galantamine is a brain selective ChEI that has negligible effects on BuChE. It exerts its therapeutic effect through allosteric modulation and by binding with nicotinic receptors. Through these mechanisms, galantamine is believed to increase the synaptic availability of ACh and in doing so it facilitates the binding of ACh molecules to its receptors. Both rivastigmine and galantamine are well tolerated in the elderly and like donepezil the most common adverse effects are nausea, diarrhea, and vomiting. Adverse effects generally occur during titration and abate once the target dose has been attained (Rivas-Vazquez, 2001).

Memantine is a moderate affinity, uncompetitive NMDA receptor antagonist that has been approved for the treatment of moderate to severe AD. It is well tolerated in the elderly and research has shown that memantine can be safely administered in conjunction with ChEI therapy (Doody, Tariot, Pfeiffer, Olin, & Graham, 2007). Adverse effects can include nausea, dizziness, constipation, headache and back pain (Rossom, Adityanjee, & Dysken, 2004). Findings for the others dementias are limited, but efficacy for treating VaD, Frontotemporal Dementia (FTD) and DLB has been demonstrated (see Swanberg, 2007; Sabbagh, Hake, Ahmed, & Farlow, 2006; Koch, Uyanik, & FischerBarnicol, 2006). However, the research has also shown that approximately 40% of people with DLB experience exacerbation of their symptoms when treated with memantine (MenendezGonzalez, Calatayud, & BlazquezMenes, 2006; Ridha, Josephs, & Rossor, 2005).

The NMDA receptor is a subtype of the glutamate receptor and it is believed to regulate synaptic plasticity and to play a significant role in learning and memory. Over stimulation of this receptor causes cell death via excitotoxicity, while blocking this receptor helps to preserve neuronal functioning (Francis, 2003). In this fashion, it is possible that memantine produces its therapeutic effect by: 1) minimizing the onset of behavioral disturbances (i.e., minimizing excitotoxicity); or 2) through the rapid blocking/unblocking of the NMDA receptors, memantine stabilizes/preserves glutamatergic function. Although the exact mechanism through which memantine reduces agitation and aggression is not known, it is likely that memantine's ability to preserve long term potentiation (LTP) and long term depression (LTD) is involved (Francis, 2003, Doody et al., 2007; Gauthier, Wirth, & Mobius, 2005).

Having conducted a detailed search of the literature no publications were discovered that specifically investigated the ChEIs or memantine as an intervention for VDB. However, two case reports were found in which transdermal nicotine (TN) was used to successfully treat incessant screaming and repetitive cries for help. In this report, Rosin et al. (2001) describe the cases of two elderly women, one diagnosed with AD and the other with VaD that displayed VDB. Both patients had previous trials of several psychotropic medications, but despite their physicians best efforts the women continued to display VDB. The patient with AD was started on 7mg of TN and 8-days later it was increased to 14mg. Following this increase, the patient's VDB was estimated to be 95% reduced. The second woman was started and maintained on 7mg of TN, which according to the authors resulted in a dramatic decrease in her vocalisations. Although the precise mechanism of action is not known, Rosin et al. (2001) did note that nicotine therapy might be an effective intervention for VDB. In this regard, it would appear that more research is needed.

Pharmacological treatment of other conditions

To date, the available research concerning the treatment of VDB is limited and what has been conducted is insufficient to offer generalizations about the larger dementia population. Having said that, clinical intuition suggests that one way to gather insight into effective treatments for VDB is to evaluate research that has investigated the symptomology of conditions other than dementia. For example, vocal disruption is also common in schizophrenia, mental retardation, and people that have experienced a cerebrovascular event (see Ramasubbu, 2003; Kim, Shin, Kim, Lim, Yang, & Yoon,

2005). In the following section two studies will be reviewed that evaluated the efficacy of mirtazapine (Remeron®) and lamotrigine as treatments for vocal disruption.

Kim et al. (2005), reported two cases of pathological laughing and crying (PLC) that were successfully treated with the antidepressant mirtazapine. Pseudobulbar affect, emotional lability or PLC is a common manifestation following stroke. It is characterized by episodes of uncontrollable laughing and/or crying that are inappropriate to the behavioral context. The mechanism that underlies this condition is believed to involve dysfunction of the serotonergic system with anatomical abnormalities in the pons, basal ganglia, cerebral cortex and the cerebellum. In addition, researchers have also speculated that the neurocircuitry that connects the frontal and temporal lobes, the basal ganglia and the basal brainstem might influence the development of PLC. In the present study, the PLC of two post stroke women, aged 63 and 64 showed rapid improvement following the introduction of mirtazapine. Previous trials of sertraline, citalopram, bupropion, valproic acid, and lorazepam were unsuccessful. One woman received a total daily dose of 45mg, while the second received a total daily dose of 15mg. In both cases the women's incidents of PLC had decreased in frequency and intensity (Kim et al., 2005).

Mirtazapine is a NaSSA (noradrenergic selective serotonin antidepressant) that is indicated for the symptomatic relief of depressive illness (Gardner, Malone, Sey, & Babington, 2004). It is well tolerated in the elderly and has been shown to be efficacious for treating depression (Versiani, Moreno, Ramakersvan Moorsel, Schutte, & Comparative Efficacy of Antidepressants Study Group, 2005; Raji & Brady, 2001). Pharmacologically, mirtazapine is a racemic mixture of two active enantiomers. The S-enantiomer blocks 5-HT_3 receptors and the R- (+) enantiomer blocks α_2-adrenergric and

the 5-HT_2 receptors. Mechanistically, mirtazapine acts by blocking central presynaptic α_2-adrenergric receptors and is antagonistic to 5-HT_{2A}, 5-HT_{2C}, 5-HT_3 and histamine (H_1) receptors (CPS, 2006). Blockade of α_2-adrenergric receptors disinhibits the NE activation of 5-HT neurons and thereby increases 5-HT neurotransmission. In addition, it is likely that H_1 antagonism and the associated somnolence, is in part responsible for mirtazapine's anxiolytic effects (Gardner et al., 2004). To conclude, the authors suggested that PLC has a underlying serotonergic dysfunction and that the rapid response to mirtazapine is similar to that observed in people who are treated for depression (Kim et al., 2005).

Ramasubbu (2003) reported the case of a 50-year old Caucasian woman who developed PLC after an ischemic stroke to her left frontal and temporal lobes. Her laughing spells were documented to occur five times per day and to last for approximately 4 to 6 minutes per incidence. Episodes of crying occurred seven or eight times per day and were noted to last for approximately three to four minutes. Her MMSE scored was 28 out of 30 and there was no history of psychiatric illness. She was started on 50mg of lamotrigine and by week six her daily dose was increased to 100mg. During the study, improvements in both laughing and crying were observed on a weekly basis, and laughing was completely absent after week four. At the end of the study, the patient's laughing was still absent and her crying was reduced to two or three times a week. In summary, the author concluded that lamotrigine could be useful as a treatment of post-stroke PLC and that the efficacy of this intervention needs to be established with double-blind placebo-controlled studies.

Lamotrigine is an antiepileptic medication that has been designed as an adjunctive therapy for adult patients with epilepsy. In terms of pharmacology, lamotrigine is thought to regulate voltage-gated sodium channels, which in turn inhibits the release of glutamate. Through this mechanism, lamotrigine is thought to minimize the generation and spread seizures (CPS, 2006). In addition to its ability to inhibit glutamate, Ramasubbu (2003) has suggested that the observed effect in this case could have resulted from inhibition of 5-HT reuptake and/or inhibition of norepinephrine and dopamine.

To conclude, studies indicate that numerous psychotropic medications are effective for treating the BPSD, but that there is insufficient empirical evidence to recommend many of these agents. Complicating matters further is that the elderly are highly susceptible to adverse effects and that because of their concomitant medical complications many are also at risk for adverse drug interactions. In regards to VDB, the research suggests that there have been few studies that have specifically investigated this condition and of the available results the sample sizes have been too small to make generalizations about the larger dementia population. To date, transdermal nicotine, trazodone, citalopram, paroxetine, and risperidone have been investigated. Each intervention has been shown to be capable of reducing VDB, but for the reasons stated above there is insufficient evidence to recommend either intervention as a treatment for VDB. Furthermore, it was readily apparent when reviewing the literature that part of the problem with determining which psychotropic medications are efficacious was that in most cases VDB was defined under the broader term of agitation as opposed to an individual BPSD. In this fashion, it could not be determined if medications that are effective for alleviating agitation are in fact effective for treating VDB. Until VDB is

investigated as an individual symptom it will continue to be difficult to determine which medications, if any, are effective for treating this debilitating condition.

CHAPTER THREE

Human Neurophysiology

The vertebrate nervous system is divided into two parts, the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS includes the brain and spinal cord, while the PNS includes all other nerves that do not lie within the CNS. Within the CNS there are billions of nerve cells called neurons. Neurons are highly specialized cells that are designed for the processing and transmitting of cellular signals. They are highly diverse and their complexity ranges from the very simple (i.e., a single dendrite) to highly complex (i.e., up to 1000 dendrites). Despite this diversity, each neuron's basic structure is the same and each is composed of a soma (also called the cell body), a dendrite (or numerous dendrites - also called a dendritic tree) and an axon (please refer to the Figure 1 given below). The soma is the central part of the neuron. It contains the nucleus and is the primary site for protein synthesis. The dendrites are cellular extensions of the soma and they function as the primary site for most cellular input. The axon is a long filament-like extension of the soma that conducts electrical impulses from the soma to a highly specialized structure at the end of the axon called the axon terminal. The axon terminal functions in the storage and release of neurotransmitters (Kaplan et al., 1994).

Neurons are classified on the basis of their polarity, functionality, direction and discharge pattern. Neurons can be unipolar, bipolar or multipolar and their function can be to excite, inhibit or modulate target neurons (please refer to Figure 2 given below). They send information from the brain (i.e., efferent), receive signals from the tissues and organs (i.e., afferent) and they can connect other neurons within a specific region (i.e.,

interneurons). Finally, neurons can be tonic (i.e., the neuron is constantly active), bursting (i.e., the neuron fires action potentials in bursts), fast spiking (i.e., the neuron fires action

Figure 1: Neuronal anatomy

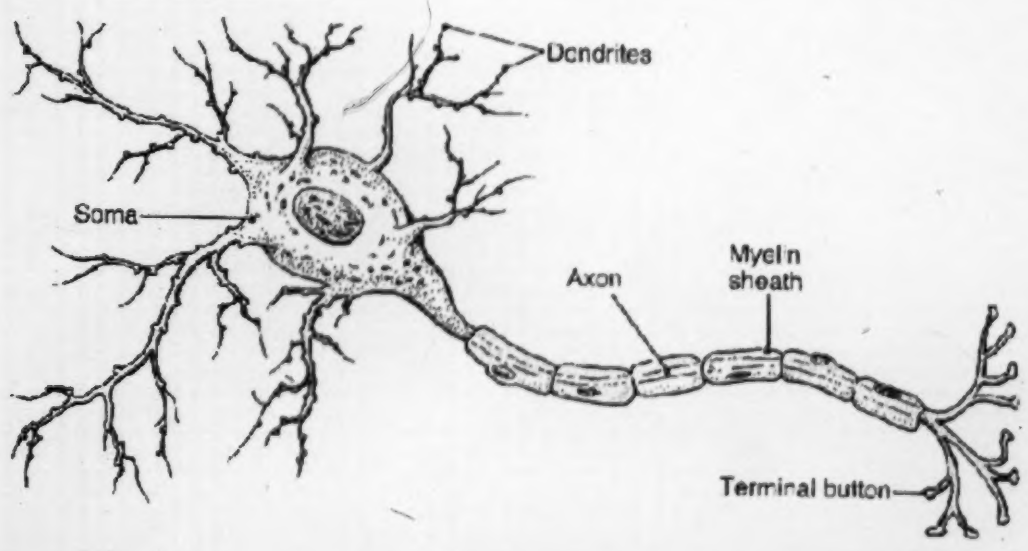

Figure Caption: Figure depicting the anatomical components of a neuron. From left to right the figure includes a cell body or soma, dendrites (i.e., structures that receive synaptic input) as well as the axon (i.e., the long filament like structure that propagates the generated action potential to the terminal button). Please note that the axon of covered by myelin (a layered tissue of lipids & protein) that acts as an insulator for the neuron and aids in the conduction of the action potential. At the far right, note the terminal button. This structure facilitates the release of the neurotransmitter (i.e., chemical messengers) into the synaptic cleft. Taken from http://www.mindcreators.com/Images/NB_Neuron.gif on November 5, 2007.

potentials at incredibly fast rates) and thin-spiked (i.e., the action potentials are narrower in relation to other neurons) (Kaplan et al., 1994).

Neurons communicate (i.e., neurotransmission) with each other via a synapse, where the axon terminal of one neuron impinges upon a dendrite of another. There are two types of synapses, chemical and electrical, of which the electrical synapse is more predominant in cold-blooded organisms. In a chemical synapse, neurotransmission starts

when a chemical substance called a neurotransmitter interacts with a receptor on the dendritic tree. If the target neuron is excitatory, this process will cause the membrane's channels, called ionophores to open and allow sodium and potassium ions to enter the

Figure 2: Illustrations of neuronal diversity

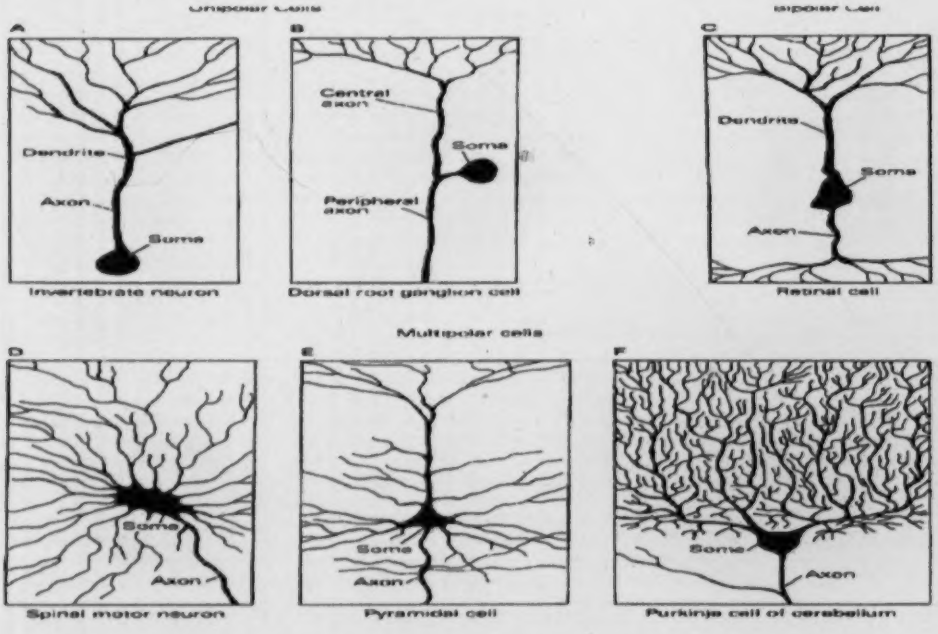

Figure Caption: Figure depicting neuronal diversity. Please note how the different neurons have dendritic processes in different locations. Some neurons, like the Purkinje cell of the cerebellum have elaborate dendritic trees at the soma, whereas other neurons (i.e., a retinal cell) have numerous dendritic processes at the pre-synaptic and post-synaptic locations of the soma. Higher numbers of dendritic processes are generally associated with neurons that served higher order processing and/or relaying of neural information. Also note the polarity of the dendritic trees. Unipolar cells have dendrites on one side of the soma, bipolar cells have dendrites on both sides, and multi-polar neurons can have dendrites anywhere on the neuron. Taken from http://www.psych.ndsu.nodak.edu/mccourt/Psy460/Neurophysiology%20of%20vision/types%20of%20neurons.JPG on November 4, 2007.

cell. Sodium and potassium are both positively charged cations and when they enter the cell it causes the resting membrane potential to become depolarized, meaning, there is an

absolute increase in the cell's electrical charge. As more cations enter the cell its membrane potential reaches a threshold where it will generate an action potential. The action potential or electrical impulse then propagates along the axon to the axon terminal where it causes the cell's ionophores to open and allow calcium cations to enter the cell. With the introduction of calcium, the synaptic vesicles, which are filled with neurotransmitter fuse with the cell membrane and release their contents into the synaptic cleft (Kaplan et al., 1994). Please see figure 3 for an illustration.

Figure 3: Illustration depicting neurotransmitter release

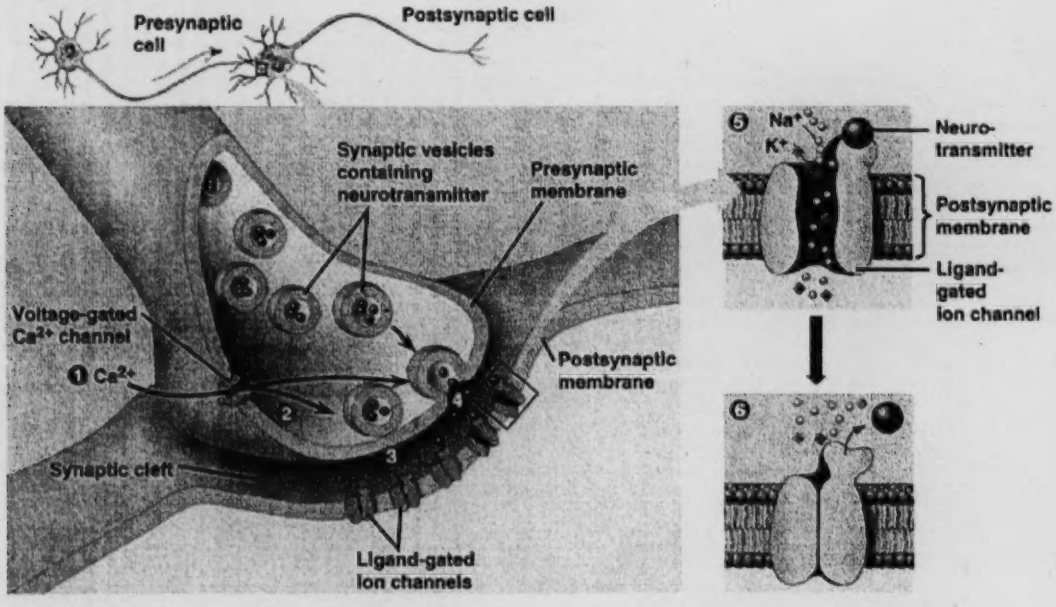

Figure Caption: Figure depicting the release of neurotransmitter into the synaptic cleft. Note the influx of calcium cations through voltage gated calcium channels that initiate the movement of the synaptic vesicles. Calcium channels open as a response to the action potential. The synaptic vesicles migrate towards the cell membrane, where they eventually fuse. Once fused to the cell membrane the synaptic vesicles release their contents (i.e., neurotransmitter) into the synaptic cleft. Taken from http://fig.cox.miami.edu/~cmallery/150/neuro/c7.48.17.synapse.jpg on November 4, 2007.

Once released, the neurotransmitter drifts across the synapse where it can interact with receptors on the postsynaptic cell, synaptic enzymes and in some cases presynaptic autoreceptors. Activating presynaptic autoreceptors will stop the release of the neurotransmitter from the presynaptic cell and synaptic enzymes will metabolize neurotransmitters while they are in the synapse. Once a neurotransmitter interacts with a postsynaptic receptor, the postsynaptic neuron will become excited, inhibited or modulated. If the postsynaptic neuron is excitatory, excitatory neurotransmitters (i.e., acetylcholine & glutamate) will cause the neuron to become depolarized and to subsequently generate another action potential. If the postsynaptic neuron is inhibitory, inhibitory neurotransmitters (i.e., GABA) will inhibit the postsynaptic neuron and cause it to become hyperpolarized (i.e., there is an influx of chloride ions, which causes an absolute decrease in the cell's electrical potential). In this state, it is more difficult for the neuron to become excited and thereby prevents it from generating an action potential. Finally, if the postsynaptic neuron is modulatory, interaction from neurotransmitters like serotonin, norepinephrine and dopamine (i.e., the neuron has serotonergic, noradrenergic and/or dopaminergic receptors) will cause the neuron to become excited or inhibited (Kaplan et al., 1994). For example, one of the pharmacological properties of the antidepressant mirtazapine (Remeron®) is that it blocks the tonic inhibition of α_2-receptor activation on dopaminergic neurons. Through this mechanism, mirtazapine is capable of increasing dopamine action potentials from the ventral tegmentum and thereby contributes to the increase of dopamine's concentration in the frontal cortex (Millan, Gobert, Rivet, Adhumeau-Auclair, Cussac, Newman-Tancredi, et al., 2000).

Review of Dementia Pathology

To date, the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition Text Revision (DSM-IV TR) recognizes 13 different classifications of dementia (American Psychiatric Association, 2000), of which AD, VaD, DLB and FTD are the most common. To be diagnosed with dementia, a person must demonstrate multiple cognitive deficits that include memory impairment and at least one of the following disturbances: aphasia, apraxia, agnosia or a disturbance in executive functioning. Furthermore, the cognitive deficits must be severe enough to cause impairments in occupational or social functioning and represent a significant decline from the individual's previous functioning (Hemels, Lanctôt, Iskedjian, & Einarson, 2001).

Once an individual has been identified as suffering from some variant of dementia, a clinician must then make a differential diagnosis to determine which type of dementia an individual is experiencing. Providing an accurate diagnosis is not only important for future treatment decisions, but it can also help caregivers to be better prepared for a patient's disease specific behaviors. For example, in the earlier stages of their illness the behavioral presentation of a person with FTD will be considerably different from someone who is diagnosed with AD. The person with FTD is much more likely to demonstrate personality changes, alterations of mood, and disinhibited behavior, whereas a person with AD is more likely to become disorientated to their new surroundings. By knowing a person's type of dementia, a caregiver can prepare for and/or anticipate many of these associated behaviors and in some cases implement preventative strategies to better manage the person's behavior (Herrmann, 2001). For example, before an individual is admitted to a long-term care facility, the caregivers could place pictures

of the patient and other memorabilia in their bedroom as well as directional signs to their bedroom on the hallway walls. Not only do such interventions help to facilitate the patient's orientation but it also makes them feel more comfortable with their surroundings and in many cases helps to reduce feelings of anxiety and agitation (Groulx, 2005).

Another important consideration when diagnosing an individual's type of dementia is determining whether or not their presentation is the result of a reversible form of dementia (i.e., a delirium or a depression). For example, individuals with a delirium can be difficult to differentiate from someone that is experiencing a DLB. Both conditions present with fluctuating cognition (FC) and without considering the symptom's onset or the duration of the FC it can be difficult to distinguish one condition from the other (Walker, Ayre, Perry, Wesnes, McKeith, Tovee, et al., 2000). For individuals with delirium the onset of their FC is usually within hours or days of a specific medical or environmental event and can last for weeks to as long as six months. For individuals with DLB the course of their FC is generally insidious and it lasts for the entire duration of their illness (American Psychiatric Association, 2000). Like delirium, elderly individuals suffering from severe depression can also present as a dementia. In many cases the two conditions are indistinguishable and they often require a neuropsychological assessment to determine which condition is responsible for the patient's presentation. For both delirium and depression, a full medical work-up, professional consultation, physical examination, detailed patient history, and laboratory investigations are crucial for ruling out the reversible forms of dementia (American Psychiatric Association, 2000).

It appears that the growing dementia population is a major public health issue and that the number of people developing dementia is increasing at an alarming rate (Hemels et al., 2001). For example, Lindsay, Sykes, McDowell, Verreault, & Laurin (2004) estimated that the Canadian dementia population had increased from 252,600 people in 1991 to 364,000 in 2001 and that by 2021 there will be 592,000 Canadian seniors with dementia. According to these numbers, approximately 2% of the Canadian population over the age of 65 years developed dementia between 1991 and 1997. The authors also noted that the prevalence of dementia increased dramatically with age and that the incidence rate between the two sexes was comparable. However, the authors did note that due to certain demographic characteristics (i.e., there are more elderly women in the population and women with dementia live longer than men), women are twice as likely to be diagnosed with dementia.

Before discussing the four dementias mentioned above it should be known that at present there is no established method for definitively diagnosing a specific type of dementia. A definitive diagnosis can only be confirmed upon autopsy or with a brain biopsy. As such, diagnoses are made on the basis of the person's behavioral presentation, the clinician's professional judgement, laboratory findings, diagnostic imaging (i.e., computerized tomography), patient/family history, and by ruling out reversible forms of dementia (i.e., delirium & depression). In addition, for suspected cases of AD and FTD a detailed family history is especially important, as both conditions appear to have a genetic component (American Psychiatric Association, 2000; Levy & Chelune, 2007).

Dementia of the Alzheimer's Type (AD)

Of the 13 different classifications of dementia, AD is the most common, making up 50 to 75 % of all diagnosed cases (Levy & Chelune, 2007). To be diagnosed with AD, the DSM-IV- TR requires that the individual demonstrate the general conditions described as well as the following criteria. 1. the course of their illness must be characterized by a gradual onset and continuing cognitive decline. 2. the person's deficits do not occur during the course of a delirium and 3. the disturbances are not better explained by another Axis I disorder (e.g., Schizophrenia). Finally, the DSM-IV TR requires that the person's cognitive deficits not be the result of another CNS condition (i.e., Parkinson's disease), systematic condition (i.e., hypothyroidism) or substance-induced (American Psychiatric Association, 2000).

In terms of the disease's progression, it is generally accepted that persons diagnosed with AD demonstrate memory impairments, disorientation and forgetfulness in the earlier stages of the illness and that as the illness progresses, alterations of mood, perceptual disturbances, physical aggression, and loss of functional independence becomes more prevalent. In the end stages, persons with AD fail to recognize their family members and with time all will become completely dependent on trained caregivers assistance for their ADLs. Furthermore, for individuals with AD as well as the other types of dementia it is generally agreed that the prevalence of the BPSD will increase as disease progresses and that every person diagnosed with dementia will display at least one BPSD during the course of their illness (Herrmann, 2001).

In AD, the underlying pathology causing cell death is the extracellular disposition of amyloid β peptide (i.e., neuritic plaques) and the accumulation of microtubule-associated hyperphosphorylated tau-proteins, which form paired helical filaments in the

neurons (i.e., neurofibrillary tangles), dendrites (i.e., neuropilthreads), and around plaques (Rivas-Vazquez, 2001). Neurofibrillary tangles and neuritic plaques typically affect the locus coeruleus (LC), hippocampus, midbrain rapine, amygdala, superior temporal cortex, inferior parietal cortex, and the periaqueductal gray, although the entire brain can be affected (Herrmann et al., 2004; Rivas-Vazquez, 2001; Parvizi, 2000). Other disease specific associations include cerebral atrophy secondary to synaptic and neuronal lesions, decreased concentrations of ACh, as well as the progressive disconnection of neuronal circuitry (Jellinger & Attems, 2007).

As the disease progresses, people with AD experience increased neuronal cell death and it appears that the density of glial cells increases as a function of this process. Glial cells, which can produce both AChE and BuChE typically provide structural support to neurons and act as scavengers of cellular debris following neuronal injury or death. When compared to controls, individuals with AD demonstrate increased density of glial cells that produce BuChE and decreased density of cells that produce AChE. As such, the levels of BuChE, which are typically very low in the cerebral cortex increase substantially and BuChE comes to replace AChE as the ACh degrading enzyme. Accordingly, individuals with AD typically experience decreased concentrations of ACh in the CNS and the cognitive deficits and behavioral abnormalities that are associated with such decreased concentrations (Rivas-Vazquez, 2001).

Vascular Dementia (VaD)

Unlike individuals with AD, VaD results from ischemic injury or sustained oligaemia to the brain regions associated with cognitive function, memory and behavior. It is generally found more in men under the age of 75 years and it is more common

amongst particular ethnic (e.g., African Americans) groups that are susceptible to cerebrovascular disease (Jellinger & Attems, 2007). The global prevalence of VaD is approximately 20% (Roman & Kalaria, 2006; Lindsay et al., 2004). In terms of disease progression, individuals with true VaD experience a stepwise deterioration in their cognitive and behavioral functioning (i.e., presumably due to an ischemic event), who typically present with abrupt changes in their cognition, mood and personality followed by a period of relative stability. It is important to note that with each successive step the person with VaD typically looses more brain function and as a result they become more dependent on their caregivers for assistance with their ADLs. In some cases such deterioration can reduce or eliminate certain BPSD, while in others, it can create or intensify a pre-existing behavior. For example, following an ischemic event some people with VaD have been reported to become apathetic, depressed, physically aggressive, or in some cases to display intense crying spells (Levy & Chelune, 2007).

To be diagnosed with VaD, the DSM-IV TR requires that the individual demonstrate the general conditions described above as well as the following criteria: 1) that the individual demonstrate neurological signs and symptoms (i.e., weakness of extremities and/or extensor planter response) or laboratory evidence indicative of cerebrovascular disease (i.e., multiple infarctions involving the cortex) that are judged to be etiologically related to the disturbance; 2) the deficits do not occur exclusively during the course of a delirium (American Psychiatric Association, 2000).

Morphologically, individuals that are diagnosed with VaD may experience focal and multifocal cerebrovascular lesions that are caused by large vessel disease, small vessel disease, strategic infarcts in the cortical and subcortical areas or vascular ischemic

brain lesions. To complicate matters further, people with VaD are still susceptible to developing AD and recent research has suggested that 30-60% of AD brains show symptoms characteristic of VaD (Jellinger & Attems, 2007).

Dementia with Lewy Bodies (DLB)

Dementia with Lewy Bodies (DLB) is a progressive dementia that must present with two of three core features, namely, visual hallucinations, fluctuating cognition (FC) and/or sensitivity to neuroleptic medications (Piggott, Ballard, Dickinson, McKeith, Perry, & Perry, 2007). Pathologically, DLB is characterized by Lewy bodies (pre α-synuclein) in the brainstem, archicortical and neocortical areas (Ziabreva, Ballard, Aarsland, Larsen, McKeith, Perry, et al., 2006; Ballard, Ziabreva, Perry, Larsen, O'Brien, McKeith, et al., 2006), as well as diffuse metabolic impairment in the entire cortex (Mirzaei, Rodrigues, Koehn, Knoll, & Bruecke, 2003). Furthermore and unlike those with AD, patients that suffer from DLB typically have fewer neurofibrillary tangles, albeit like AD, people with DLB also have senile plaques (Ballard et al., 2006).

To be diagnosed with DLB, the DSM-IV TR requires that the individual possess the general conditions described above as well as the demonstration of visual hallucinations, FC and/or sensitivity to neuroleptic medications. To date, there is no definitive test to diagnose DLB. As such, clinicians have to rely of their clinical judgement and other pieces of pertinent information (i.e., diagnostic imaging, laboratory investigations & patient histories) to determine whether or not a person can reasonably be diagnosed with DLB. At present, DLB is classified under the condition of Dementia due to Other General Medical Conditions (American Psychiatric Association, 2000).

In terms of behavioral/psychiatric symptoms, individuals diagnosed with DLB are more likely to experience delusions, visual, auditory and olfactory hallucinations, whereas delusions are more common in persons with AD. Furthermore, these delusions are generally secondary to poor memory whereas delusions in DLB are generally related to perceptual difficulties and/or visual hallucinations (Levy & Chelune, 2007). In addition, both individuals with DLB and AD are equally as likely to display physical aggression, verbal aggression, wandering and symptoms of depression. As such, the symptom of FC and the presence of hallucinations (i.e., visual, auditory or olfactory) have become the hallmark for differentiating DLB from the other types of dementia. For example, in persons with DLB, prevalence rates of fluctuating cognition have been reported to range from 80% - 90%, while for those with AD, the prevalence of FC typically ranges from 20% – 25% (Walker et al., 2000).

Frontotemporal Lobar Dementia (FTLD)

FTLD refers to a group of neurodegenerative disorders that are characterized by relatively focal involvement of the temporal and frontal lobes. To date, three types have been identified, which include FTD, Semantic Dementia (SD), and Progressive Nonfluent Aphasia (PNA). Of these, FTD is the most common, accounting for 10% to 20% of all neurodegenerative dementias (Levy & Chelune, 2007). In general, it is characterized by a marked disturbance in personality and social conduct that is generally associated with bilateral frontal atrophy. Anatomically, individuals with FTD are characterized by the presence of ubiquitin-positive, tau α-synuclein – negative intracellular inclusions that involve the frontal and temporal cortices as well as the dentate gyrus of the hippocampus (Whitwell, Josephs, Rossor, Stevens, Revesz, Holton, et al., 2005).

Like DLB, FTD is also classified under the condition of Dementia due to Other General Medical Conditions (American Psychiatric Association, 2000). To diagnosis a person with FTD, the DSM-IV TR requires that the person meet all the general conditions given above as well demonstrate emotional blunting, personality changes, disinhibition, lack of empathy, neglect for personal hygiene, and/or hyperorality (Levy & Chelune, 2007). As with the other dementias a detailed medical work-up, diagnostic imaging, laboratory investigations and family history are crucial for making a diagnosis of FTD (American Psychiatric Association, 2000). In addition, individuals who are diagnosed with FTD generally experience an earlier onset than the other dementias, although early onset is also possible in persons with AD (Levy & Chelune, 2007).

The pathology of dementia has been well documented in the literature and in today's society much is known about the gross anatomical abnormalities and deficits that comprise these illnesses. Despite these advances, many researchers believe that we are still not prepared to deal with the implications of our aging population, and that if we are going to address this issue, we must continue to investigate the neural mechanisms that underlie these debilitating conditions (Levy & Chelune, 2007). Thus, a review of the neural circuitry of human vocalisation will be presented, followed by a review with an examination of the neurotransmitter abnormalities that are characteristic of the aforementioned dementias.

Human Vocalisation

In general, human vocalisation is the direct result of a complex series of neural impulses that are generated in response to some sort of stimulation from the speaker's environment (i.e., internal, external or both). Once a neural impulse is generated, the

cerebral cortex evaluates the neural message, integrates the message with other neural information (i.e., emotional stimuli, input from the speaker's memory as well as the speaker's motivation to speak) and determines whether or not a verbal response is appropriate for the specific situation. Having determined that a verbal response is appropriate, the cerebral cortex initiates a series of neurological processes that causes the diaphragm to force a column of air out of the lungs. As the air flows from the lungs towards the mouth it passes through the structures of the throat, such as the larynx, and oral cavity where it is manipulated in such a way as to produce the sounds of speech. As the sounds are produced the cerebral cortex receives sensory input from the auditory cortex and proprioceptive input from the phonatory motoneurons so that it can monitor speech and control speech processes such as pitch, rhythm and articulatory accuracy (Hulit & Howard, 2006; Kaplan et al., 1994). These processes and the underlying neural mechanisms are described below.

The human brain (i.e., the midbrain and the cerebral cortex) is split into two hemispheres that are connected by a band of tissue called the corpus callosum. The corpus callosum allows the two hemispheres to communicate with one another and is crucial for normal human functioning. In regards to speech and language, it is generally accepted that the left hemisphere has more responsibilities than the right, but that the right hemisphere is crucial for processing the emotional content that underlies speech. There is also evidence to suggest that the melodic patterns we superimpose on speech when we sing are associated with the right hemisphere (Hulit & Howard, 2006).

Once a stimulus is received from the environment, the cerebral cortex transfers the sensory information to the left temporal lobe (i.e., Wernicke's area) where it is

decoded and the appropriate neural messages for a response are generated. From here, the neural messages travel to the opercular and inferior frontal gyrus (i.e., Broca's area) via a bundle of fibers called the arctuate fasciculus. In Broca's area the neural messages are organized into the appropriate articulatory motor sequence and from Broca's area they are transferred via the pyramidal neural pathways to the cerebellum (Hulit & Howard, 2006).

The cerebellum is a region of the brain that plays an important role for integrating sensory perception with motor output. In order to facilitate this role the cerebellum is constantly receiving sensory information about the status of the muscles and limbs of the body via the pyramidal and extrapyramidal pathways. Using this steady flow of information to and from the cerebral cortex, the cerebellum in combination with the basal ganglia makes crucial adjustments to the neural commands to ensure that the final motor movements are performed as accurately as possible (Hulit & Howard, 2006).

Cerebellar input is excitatory, while input from the basal ganglia is inhibitory. The information from each structure is relayed through the thalamus to the cerebral cortex and from the cerebral cortex neural messages are returned to each structure via specific neural pathways (please see Figure 4 below). From the cerebellum, neural messages are transferred to the cerebral cortex via the cerebellothalamocortical pathway and back to the cerebellum via the corticopontocerebellar pathway. From the basal ganglia inhibitory input is transferred to the thalamus from the globus pallidus interna and the substantia nigra via the pyramidal and extrapyramidal pathways (i.e., indirect and direct activation of the cerebral cortex). From the cerebral cortex neural input is relayed back to the striatum which then projects to the globus pallidus interna, globus pallidus externa, and

the substantia nigra (Kaplan et al., 1994). In this manner the control over motor function is similar to that of operating an automobile, whereby input from the cerebellum would be comparable to accelerating and input from the basal ganglia would be comparable to applying the brake. Accordingly, the delicate balance between accelerating and braking would produce the desirable rate of speed and by analogy the appropriate motor input that is necessary for specific vocalisations.

Figure 4: Diagram representing neural input to and from the cerebral cortex

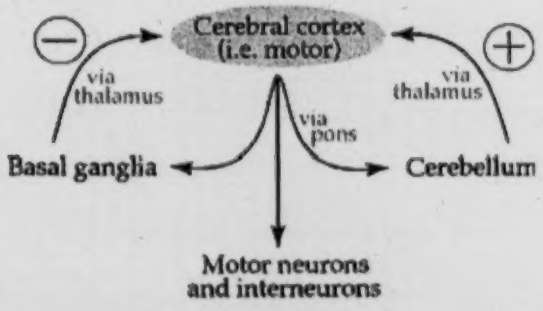

Figure Caption: This figure represents in schematic form, the excitatory neural pathway (i.e., motor) from the cerebellum via the thalamus to the cerebral cortex and from the cerebral cortex via the pons the cerebellum. The latter are referred to as the cerebellothalamocortical and corticopontocerebellar pathways respectively. Also note the pyramidal pathway that travels from the cerebral cortex to motor neurons (i.e., phonatory motoneurons). Also depicted are the inhibitory neural pathways that travel from the basal ganglia via the thalamus to the cerebral cortex. Taken from http://thalamus.wustl.edu/course/cerebell.html February 27, 2008.

The pyramidal pathway consists of a massive band of axons that links the cerebral cortex and the spinal cord. This band is comprised of the lateral corticospinal tract and the medial corticospinal tract. Both tracts function to control the spinal and cranial nerves and thereby the motor neurons in the spinal cord and torso. Cranial nerves function as sensory nerves (i.e., afferent), motor nerves (i.e., efferent), and as a combination of both

functions (i.e., sensory & motor). Of the 12 cranial nerves, only six are connected with motor speech (please see Figure 5 given below).

Spinal nerves on the other hand are all of mixed function and of the 30 pairs, over half are involved in complex neural circuitry that controls and monitors respiration. The corticobulbar tract is another pyramidal pathway that is important for the production and monitoring of speech. Its function is to connect the cerebral cortex with the brainstem

Figure 5: Pyramidal fibers serving as motor cranial nerves of speech

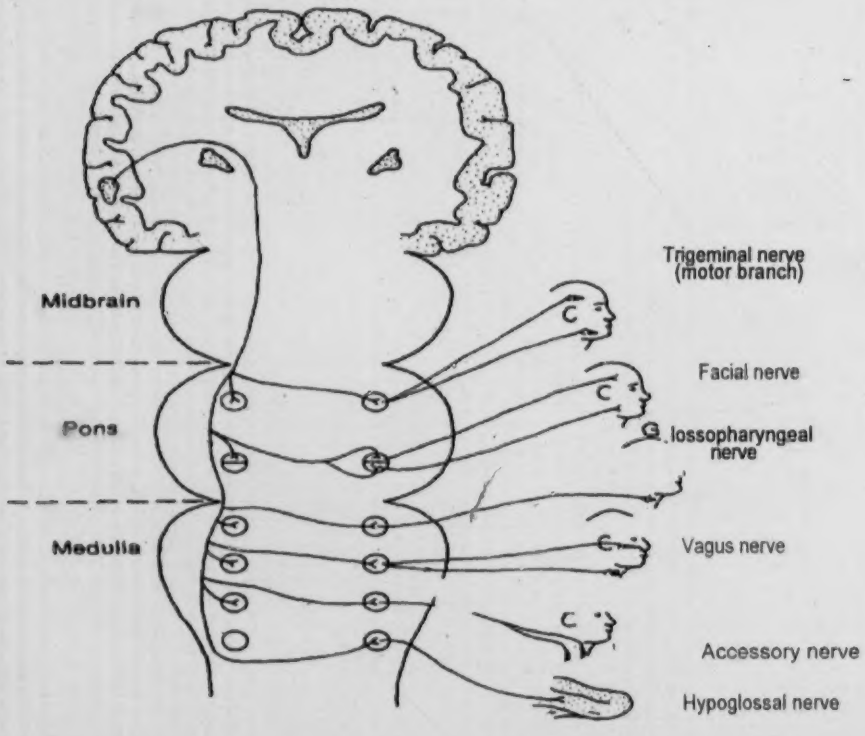

Figure Caption: Illustration depicting the pyramidal pathways that serve as the motor and cranial nerves of speech. Reprinted from Hulit, Lloyd. M., & Howard, Merle. R. (2006). *Born to Talk: An introduction to speech and Language Development. (4th Rev. Ed.). Boston, MA: Allyn and Bacon.* p. 455.

(i.e., the medulla and the pons) and through the medulla and the pons, the corticobulbar tract facilitates the cerebral cortex's control over the fine motor movements of the face, neck and tongue. For example, the hypoglossal or twelfth cranial nerve nucleus receives its input from the cerebral cortex (via the corticobulbar tract) at the medulla. From the medulla the hypoglossal nerve relays neural messages to the phonatory motor nuclei that control the tongue (Hulit & Howard 2006; Kaplan et al., 1994).

Unlike the pyramidal pathways, the extrapyramidal pathways include all tracts and brain structures that modulate motor activity without directly innervating the motor neurons. Modulating structures that involve the extrapyramidal system include the nigrostriatal pathway, the basal ganglia, and the cerebellum. In this fashion, the extrapyramidal system is responsible for gross motor movements and is typically involved in behaviors such as postural control and locomotion. For example, when we write a paragraph the extrapyramidal pathway would get the writing hand to the paper, whereas the pyramidal pathway would enable the fine motor movements that are necessary to write the letters, words and sentences. Extrapyramidal pathways are typically found in the reticular formation of the pons and medulla, and target neurons in the spinal cord (Hulit & Howard 2006; Kaplan et al., 1994).

Knowing how the brain receives sensory input, decodes sensory information, and transfers it into an appropriate motor response the following will briefly review how sounds are actually produced. In essence, human speech is the result of respiration, phonation, resonation, and articulation. Respiration or breathing provides the power for speech. It occurs when the speaker forces a column of air from the lungs through the larynx. As air passes through the larynx the process of phonation occurs, whereby the

vocal cords are drawn together via specific muscle contractions and the exhaled air causes the cords to vibrate the air column. As the exhaled air passes through the mouth, nose and other oral cavities it resonates and the tone from the vibrating vocal cords is modified according to the shape and size of the resonating cavities. From here the vibrating and resonating air column passes through the mouth, the tongue, teeth and other oral structures where the air stream is broken down into the sounds of speech (Hulit & Howard 2006).

Although the above description portrays human vocalisation as a somewhat simplistic process, it is in fact quite complex and neuroimaging studies have shown that it relies on numerous anatomical areas to produce both voluntary (planned) and involuntary (innate) utterances (Jűrgens, 2002). Involuntary or visceromotor speech is the simplest. It involves innate reflexes that are genetically pre-determined and usually occur in response to painful stimuli. The most complex, as discussed above is voluntary speech, which not only involves the voluntary initiation and suppression of sound but also the regulation of acoustic structure and the specific meaning of vocal utterances (Jűrgens, 2002). Each type differs in its complexity but both occur as a series of behavioral movements that are facilitated by the periaqueductal gray (PAG) of the midbrain rapine and the nuclei that laterally border the tegmentum. The difference is that unlike voluntary vocalisation, innate reflexes do not require the intactness of the forebrain (Jűrgens, 2002). Please see Figure 6 given below for an illustration of the PAG.

In regards to visceromotor vocalisation, the research suggests that the PAG serves a gating rather than a pattern-generating function (Jűrgens, 2002), and that when it is lesioned along with the lateral bordering tegmentum, humans experience complete

mutism (Esposito, Demeurisse, Alberti, & Fabbro, 1999). Taken together these areas and their associated projections facilitate laryngeal activity, respiratory movements, supralaryngeal activity (Jűrgens, 2002) and are important in pain processing, breathing,

Figure 6: Human midbrain showing the Periaqueductal Gray (PAG)

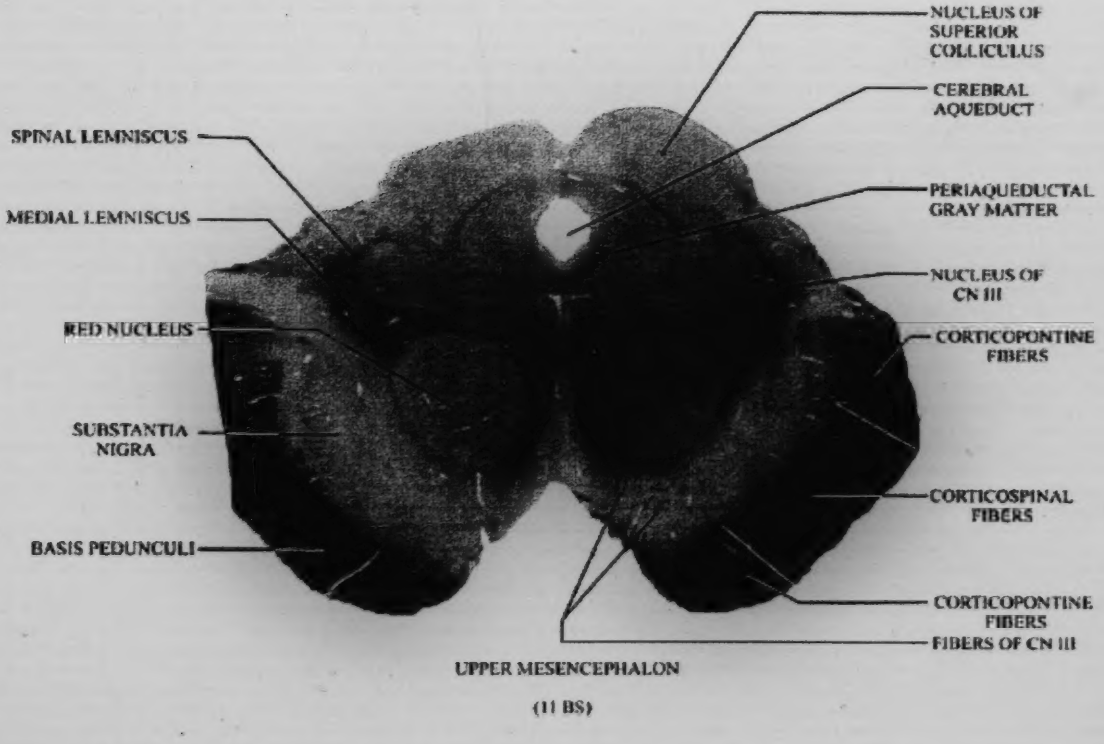

Figure Caption: Figure depicting the periaqueductal gray (PAG) of the midbrain rapine. Taken from http://www.anatomy.dal.ca/Human_Neuroanatomy/B_stem_Atlas/10BS_F.jpg on April 26, 2008.

anxiety, and panic (Esposito et al., 1999; Schulz, Varga, Jeffires, Ludlow, & Braun, 2005). In addition, neuroanatomical studies with squirrel monkeys have demonstrated

that motivation-controlling brain structures such as the amygdala, the middle thalamus, and the anterior cingulate cortex have direct projections to the PAG (Schulz et al., 2005). Alternatively, stimulation and lesion studies have demonstrated that the output projections descend along the medial edge of the lateral lemniscus into the ventrolateral pons and from here they project into the periambigual reticular formation. The periambigual reticular formation projects onto the trigeminal motor nucleus and is responsible for jaw control and lip movements (Esposito et al., 1999).

Unlike involuntary speech, voluntary speech requires the intactness of the forebrain (i.e., the mediofrontal cortex). The mediofrontal cortex is composed of the anterior cingulate gyrus, the supplementary motor area and the pre-supplementary motor area. From the mediofrontal cortex, the neural messages are transferred to the motor cortex via the pyramidal, corticobulbar and extrapyramidal pathways, whereby indirect input from the putamen, substantia nigra, parvocellular reticular formation, and the phonatory motoneurons is crucial. The motor cortex provides the appropriate motor input to the targeted muscles and it monitors the motor tasks that are being performed. To accomplish these tasks the motor cortex requires proprioceptive input from the phonatory organs, input from the ventral premotor and prefrontal cortex (i.e., Broca's area) as well as the supplementary and pre-supplementary motor areas (Jűrgens, 2002).

Based on the above, the research suggests that there are several key anatomical brain areas and neural pathways that are important for the production and monitoring of human vocalisation. These include the cerebral cortex, cerebellum, primary and supplementary motor cortex as well as the PAG. Other important structures include the thalamus and numerous subcortical structures (i.e., midline thalamus, basal ganglia,

amygdala, and several hypothalamic areas), the pons and the medulla as well as the phonatory motor neurons. These structures are controlled via an intricate communication network between the neocortex and cerebellum that includes both the pyramidal and extrapyramidal pathways. Any damage to these pathways or to the associated anatomical areas can result in numerous types of vocalisation disturbances. For example, if the ventro-lateral thalamic nuclei are inhibited or destroyed vocal control is severely impaired and vocalisations become breathy, jittery and monotonous (Jűrgens, 2002). Alternatively, lesions to the PAG have been demonstrated to produce complete mutism in humans, while in animal models stimulation of the PAG produces erratic and uncontrollable vocalisations (Dujardin & Jűrgens, 2006). Based on this association and considering that the PAG has been shown to act as a link between the emotional-motivational structures of the forebrain and motor articulatory structures associated with the periambigual formation, it is likely that the PAG is in part involved in the pathogenesis of VDB. It is important for the initiation of vocalisation and it is believed to be crucial for facilitating the emotional content of speech. Furthermore, neuroimaging studies have demonstrated that areas of the temporal lobe and the cerebellum are co-activated with the neocortex and the PAG, which suggests that these structures may support vocal self-monitoring. Taken together, these areas may represent a neuroanatomical circuit that regulates the production and feedback of speech-related vocalisation (Schulz et al., 2005).

NEUROTRANSMITTERS

Neurotransmitters & Dementia

For people with dementia there are numerous gross disruptions to their neuronal functioning. Such disruptions can include atrophy of brain tissue, alterations to neural circuitry as well as abnormal production and functioning of neurotransmitters. Each of these abnormalities can contribute to an individual's demonstration of BPSD, but unlike atrophy of brain tissue and dysfunctional neural circuitry, only neurotransmitter dysfunction is amenable to human intervention. Accordingly, current research on the treatment of dementia is investigating the relationship between neurotransmitter dysfunction and the demonstration of specific types of behavioral disturbances (Herrmann & Lanctôt, 2007). With this approach, many researchers have speculated that future research will not only be able to provide key information about pharmacological treatment options but it will also enable a physician to treat their patients more effectively. Any improvement in these behaviors no matter how modest can result in a significant improvement in a patient's quality of life and thereby deserves our continued attention and investigation (Herrmann & Lanctôt, 2007).

To date, acetylcholine (ACh) has been the most studied neurotransmitter, but serotonin (5-HT), norepinephrine (NE), dopamine (DA) and gamma-aminobutyric acid (GABA) have been gaining considerable recognition as contributors to the BPSD (for a review see Herrmann & Lanctôt, 2007; Huey, Putnam, & Grafman, 2006; Lanari, Amenta, Silvestrelli, Tomassoni, & Parnetti, 2006). In the following review, the author will discuss these neurotransmitters and provide the reader with a description of each neurotransmitter, how they are synthesized, their associated neural pathways and how each is related to the BPSD.

Serotonin (5-HT)

Serotonin or 5-hydroxytryptamine (5-HT) is an indoleamine neurotransmitter that is derived from the essential amino acid tryptophan (Trp). Trp is obtained from the diet and is typically found in foods like milk, fish, turkey and chocolate. Once ingested, Trp crosses the blood brain barrier to the midbrain rapine where it is hydroxylated into 5-hydroxytryptophan (5-HTP). 5-HTP is then decarboxylated to 5-HT and stored in the synaptic vesicles. 5-HT's enzymatic processes occur through monoamine oxidase (MAO) and its primary metabolite is 5-hydroxyindole acetic acid (Kaplan et al., 1994).

In terms of neurotransmission the central serotonergic system is known to follow one of two pathways that both originate in the midbrain rapine. The caudal nuclei project to the cerebellar cortex and spinal cord, while the rostral nuclei project to the limbic system, hypothalamus, thalamus, hippocampus and frontal cortex (please refer to Figure 7 given below). In terms of receptors, seven types have been identified. These include 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7, of which 5-HT_1 and 5-HT_2 has receptor subtypes (Kaplan et al., 1994).

For those with dementia the research has demonstrated that there is a decrease in the availability of 5-HT in the midbrain rapine and 5-hydroxyindole acetic (5-HIAA) in the basal ganglia. Such decreases have been associated with depression, anxiety, agitation, psychosis, aggression, and sleep disturbances (Lanctôt, Herrmann, & Mazzotta, 2001). In regards to serotonergic receptors, the research has indicated that the 5-HT_{1A} receptor is mainly expressed presynaptically in the midbrain, while postsynaptic expression is evident in the hippocampus, brainstem, frontal cortex, basal ganglia, as well as the cerebellum (Lanctôt et al., 2001; Richter, Manzke, Wilken, & Ponimaskin, 2003).

The 5- HT_{1A} receptor has been implicated in depression, suicidal behavior, aggression, breathing, and learning (Lai, Tsang, Francis, Esiri, Keene, Hope, et al., 2003; Richter et al., 2003). In regards to dementia, the research indicates that the 5-HT_{1A} receptor and 5-HT_{1A} receptor binding is significantly reduced in the cortex, hippocampus and amygdala of persons with AD and FTD (Lai et al., 2003; Lanctôt et al., 2001; Lanctôt,

Figure 7: Illustration depicting sertoninergic neural pathways in the human brain

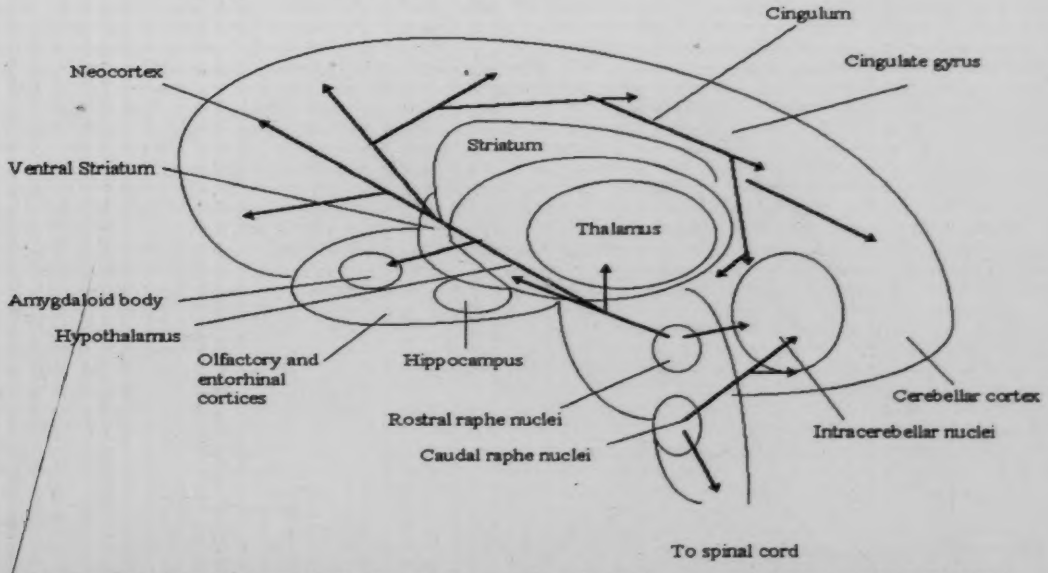

Figure Caption: Figure depicting the serotonergic pathways of the human brain. The central serotonergic system is known to follow one of two pathways that both originate in the midbrain rapine. The caudal nuclei project to the cerebellar cortex and spinal cord, while the rostral nuclei project to the limbic system, hypothalamus, thalamus, hippocampus and frontal cortex. Taken from http://pages.cs.wisc.edu/~caitlin/papers/Prozac/6.gif on February 4, 2008

Herrmann, Ganjavi, Black, Rusjan, Houle, et al., 2007). With the exception of the 5-$HT_{1D\beta}$ receptor the function on the remaining 5-HT_1 receptor subtypes is still being elucidated (Lanctôt et al., 2001; Sari, 2004). To date, the research has indicated that the 5-$HT_{1D\beta}$ receptor is associated with anxiety, depression as well as aggression and that it is

expressed in the ventral pallidum, globus pallidus, substantia nigra as well as the deep nuclei of the cerebellum (Sari, 2004).

There are three subtypes of the 5-HT_2 receptor, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}. The 5-HT_{2A} receptor is found postsynaptically on non-serotonergic neurons in the neocortex, claustrum and basal ganglia where it suppresses the median prefrontal firing and synaptic release of glutamate, DA, NE and ACh. They are associated with the regulation of slow wave sleep and endocrine responses. Behaviorally, the 5-HT_{2A} receptor has been associated with anxiety, depression, migraine headaches, and psychosis (Naughton, Mulrooney, & Leonard, 2000). The 5-HT_{2B} receptor is also expressed postsynaptically, but unlike the 5-HT_{2A} receptor, 5-HT_{2B} is found primarily in the limbic system and the hypothalamus. Behaviorally, the 5-HT_{2B} receptor has been associated with depression, sleep disturbances and hallucinations (Lanctôt et al., 2001). The 5-HT_{2C} receptors are also found postsynaptically on non-serotonergic neurons. Research has shown that these receptors are involved in cerebral spinal fluid production, hypolocomotion, hypophagia, and that they are expressed in the choroid plexus, substantia nigra, globus pallidus, and the cerebral cortex (Naughton et al., 2000).

Research has shown that abnormalities of the 5-HT_2 receptor are found in both the frontal and temporal lobes of people with AD (Lai, Tsang, Alder, Keene, Hope, Esiri, et al, 2005) and that such abnormalities are associated with anxiety, depression, and psychosis (Naughton et al., 2000). Furthermore, research by Lai et al. (2005) has shown that the loss of 5-HT_{2A} receptors in the neocortex might predict rate of cognitive decline in persons with AD, whereby 5-HT_{2A} receptor densities are correlated with patient's MMSE scores. In addition, the research has also shown that as AD progresses, the loss of

5-HT_2 receptors becomes greater than that of the 5-HT_1 receptors, which suggests that individual's with these pathologic characteristics are at risk for developing visual hallucinations (Lanctôt et al., 2001).

The relationships between the remaining 5-HT receptors and behavioral disorders seen in AD and dementia are not as well defined. The 5-HT_3 receptor is found postsynaptically in the amygdala, frontal cortex and hippocampus, while 5-HT_4 receptors are found in the basal ganglia, hippocampus, and the limbic system (Naughton et al., 2000; Lanctôt et al., 2001). Both have been shown to be associated with anxiety and psychosis, and the 5-HT_4 receptor has also been linked to generating the respiratory rhythm (Richter et al., 2003), sleep disturbances, learning deficits and cognition (Lanctôt et al., 2001). In regards to dementia, the loss of the 5-HT_3 & 5-HT_4 receptor has not been investigated and the function and location of remaining serotonergic receptors have yet to be elucidated (Lanctôt et al., 2001).

In summary, the research finds that for individuals with dementia there is a significant reduction in the overall functioning of their serotonergic system and that such reductions are observed as reduced receptor densities and 5-HT concentrations. These findings have been identified in AD, subtypes of VaD, FTD and DLB (Lanctôt et al., 2001; Huey et al., 2006; Lanctôt et al., 2007). Furthermore, it should also be noted that serotonergic neurons like many other neurons are modulated by other neurotransmitters and that some of the BPSD might arise from deficits within the serotonergic system that are precipitated by another modulating neurotransmitter (Herrmann et al., 2004).

Norepinephrine (NE)

NE is a chemical compound that can act as a catecholamine neurotransmitter or as a hormone. In the United Kingdom and Europe, NE is called noradrenaline, while in North America it is called norepinephrine. Hormonal NE is released from the adrenal medulla into the blood stream where it interacts with alpha (α) receptors and beta (β) adrenergic receptors to help control arousal, blood pressure, mood, and the fight or flight response. As a neurotransmitter, NE is stored and released from noradrenergic neurons where it also interacts with α receptors, β receptors, as well as two types of synaptic enzymes. Enzymatic processes occur through catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO) to form 3-methoxy-4-hydroxyphenylglycol (MHPG) and other metabolites (see Kaplan et al., 1994; Herrmann et al., 2004).

In regards to receptor properties, α-receptors are excitatory, while the β receptors are inhibitory. Each type of receptor has receptor subtypes and these have been shown to include α_{1A}, α_{1B}, α_{1D}, α_{2A}, α_{2B} and α_{2C}, as well as β_1, β_2, and β_3. α_1-receptors are expressed postsynaptically, while α_2- and β_2-receptors are expressed pre and postsynaptically (Herrmann et al., 2004). Within the central nervous system the observed clinical effect of a noradrenergic medication will depend on the availability and balance of these receptors. For example, blockade of α_1 – receptors is commonly associated with sedation and postural hypotension, while α_2 -receptor activation leads to down-regulation and inevitably to the decreased production of NE (Peskind et al., 2005).

NE is derived from the amino acid tyrosine (4-hydroxyphenylalanine) and is typically found in foods like milk, fish and turkey. When it is ingested tyrosine is converted to $_L$-dihydroxyphenylacetic acid ($_L$-DOPA) by tyrosine hydroxylase at which point it is able to cross the blood brain barrier. Once in the brain, aromatic amino acid

decarboxylase converts L-DOPA to dopamine (DA). Once DA is transported into noradrenergic neurons it is converted to NE by dopamine beta hydroxylase (see Kaplan et al., 1994; Herrmann et al., 2004).

In terms of neurotransmission, the central noradrenergic system is known to follow one of two pathways. One originates in the ventrolateral tegmentum and is involved in sexual and feeding behaviors. From the tegmentum it projects to the forebrain and is proposed to control rage and aggression. The second pathway originates in the locus coeruleus (LC) and projects to the cerebellum, thalamus, hypothalamus and the midbrain (please refer to Figure 8 below). For people with AD there is a significant decrease in noradrenergic neurons in the LC and such disruption to the noradrenergic system has been suggested to underlie the pathology of the disease. These findings have also been demonstrated with DLB, but for those with FTD and VaD the research suggests that their noradrenergic system is relatively intact (Szot, White, Greenup, Leverenz, Peskind, & Raskind, 2006; Herrmann et al., 2004; Huey et al., 2006).

The LC is involved in the regulation of arousal, the flight or fight response, agitation, anxiety, vigilance, and emotion. Research has shown that the loss of noradrenergic neurons in the LC may lead to a compensatory up-regulation of the remaining NE neurons, which amongst other things causes an increase in the overall activity of the noradrenergic system (Matthews, Chen, Esiri, Keene, Minger, & Francis, 2002). As a result, the person with AD is in a heightened state of physiological arousal, whereby such stimulation it likely to precipitate wandering, physical aggression and/or agitation (Herrmann et al., 2004). Similarly, there is a well-established link between the severity of AD and the loss of noradrenergic neurons in the LC, whereby the levels NE

are inversely proportional to the severity of the patient's cognitive impairment. Considering that many people with moderate to severe dementia demonstrate at least one BPSD, it is likely that the increased concentrations of NE or an abnormality to the noradrenergic system are the underlying cause of the person's behavior (Herrmann et al., 2004).

Although the information described above clearly supports the involvement of the noradrenergic system in the BPSD, most of the support comes from the studies of physical aggression and agitation. Research has identified that there is a small but significant increase in the total β-receptor concentration in the cerebella of aggressive AD patients (Herrmann et al., 2004). The latter provides a plausible explanation for aggressive behaviour, especially when pharmacological research has demonstrated that physically aggressive behavior responds to β-receptor blocker pharmacotherapy (Peskind et al., 2005; Herrmann et al., 2004). Similarly, postmortem research has demonstrated that there are significantly elevated levels of α_2–adrenoreceptors in the cerebellum of aggressive participants with AD, when compared to non-agitated AD controls. Since presynaptic α_2–adrenoreceptors regulate the negative feedback of NE and postsynaptic receptors are thought to regulate postsynaptic neuronal function, it is likely that the differing locations of α and β receptors play a key role in modulating physical aggression (Herrmann et al., 2004).

The involvement of the noradrenergic system in the BPSD is further supported by consideration of the possible pathophysiological mechanism of agitation. For example, when participants with AD are treated with yohimbine, a α_2–adrenoreceptor antagonist, they typically display more agitated behaviors than elderly controls. In addition, there

Figure 8: Illustration depicting noradrenergic neural pathways in the human brain

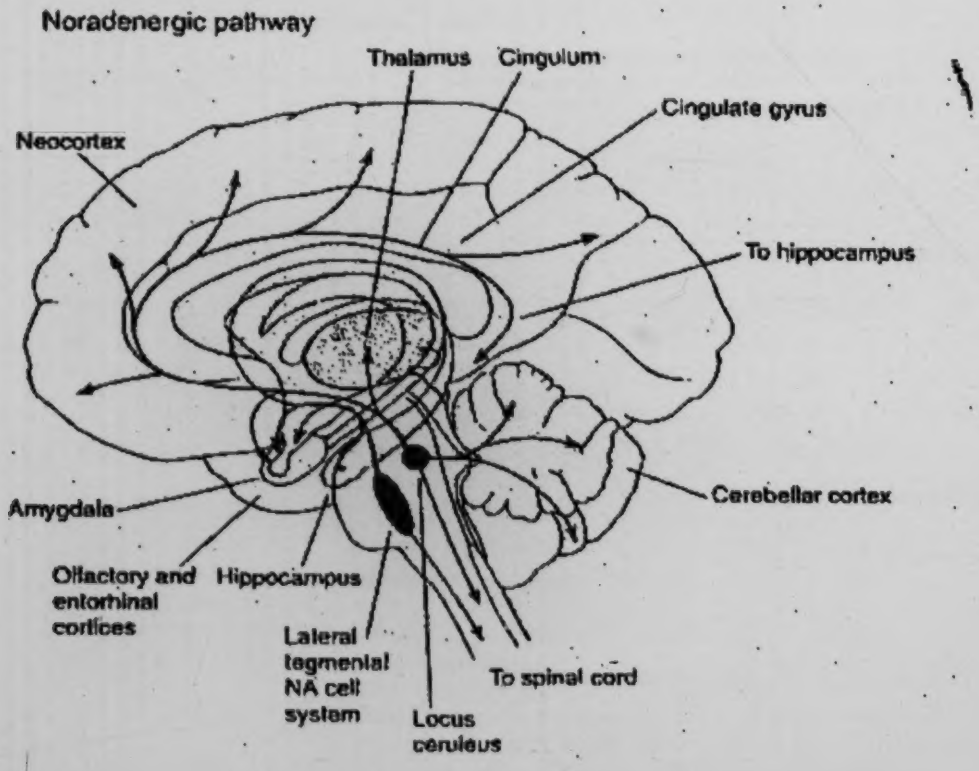

Figure Caption: Figure depicting the noradrenergic pathways of the human brain. The central noradrenergic system is known to follow one of two pathways. One originates in the ventrolateral tegmentum. From the tegmentum the noradrenergic pathway projects to the forebrain. The second pathway originates in the locus coeruleus (LC) and projects to the cerebellum, thalamus, hypothalamus and the midbrain. Taken from http://www.benbest.com/science/anatmind/FigX20.gif on February 4, 2008

appears to be an association between motor restlessness and increased levels of MHPG, which suggests that there is an increase in the postsynaptic sensitivity of NE. This finding seems plausible, as postsynaptic β-receptors have been shown to be up-regulated in the prefrontal cortex and hippocampus of patients with AD (Herrmann et al., 2004).

In summary, the research has demonstrated that noradrenergic dysfunction contributes to the pathology of physical aggression, agitation and anxiety in AD. The

research has also indicated that patients with DLB experience similar changes to those with AD, while for those with VaD and FTD the research suggests that their noradrenergic system is relatively intact (Szot et al., 2006; Huey et al., 2006). Finally, it should be noted that noradrenergic neurons like many other neurons are modulated by other neuro-chemicals (i.e., 5-HT, ACh, GABA and DA). A loss or alteration in any of these neurotransmitters is likely to affect NE and potentially lead to deviations in a person's behavior (Herrmann et al., 2004).

Dopamine

Tyrosine (4-hydroxyphenylalanine) is an amino acid that is typically found in foods like milk, fish and turkey. When it is ingested tyrosine is converted to $_{L}$-dihydroxyphenylacetic acid ($_{L}$-DOPA) by tyrosine hydroxylase at which point it is able to cross the blood brain barrier. Once in the brain, aromatic amino acid decarboxylase converts $_{L}$-DOPA to dopamine (Herrmann et al., 2004). Postsynaptically, enzymatic processes occur through catechol-O-methyl transferase (COMT), MAO_A and MAO_B to form homovanillic acid (Dunlop & Nemeroff, 2007).

Dopaminergic receptors are divided into two families and include D_1 and D_2 receptor subtypes. The D_1 family includes D_1 and D_5 receptors while the D_2 family includes D_2, D_3 and D_4. Both types are expressed pre and postsynaptically and are differentiated from one another by their mechanisms of transduction. For example, the D_1 receptors appear to be linked to adenylate cyclase (AC) activation, whereas the D_2 receptor is related to AC inhibition (Kaplan et al., 1994). The D_1 family is excitatory and these receptors are expressed in the dorsal and ventral striatum as well as the hypothalamus and thalamus. More specifically, the D_1 receptor is found on GABAergic

neurons that project to the substantia nigra, while the D_5 receptor is expressed in the hypothalamus and thalamus. Alternatively, the D_2 family is inhibitory and these receptors are expressed in the dorsal and ventral striatum. The D_3 receptor is found within the ventral striatum and nucleus accumbens, while the D_4 receptors are mainly expressed in the frontal cortex, amygdala and hypothalamus (Kaplan et al., 1994; Dunlop & Nemeroff, 2007).

Most DA-producing neurons are located in the brain stem nuclei. The axons of these nuclei originate in the retro-rubro field, the substantia nigra pars compacta and the ventral tegmental area (VTA). From here, the axons project along three different pathways via the medial forebrain bundle to innervate specific cortical and subcortical structures. These include the mesolimbic, mesocortical and the nigrostriatal pathways. The nigrostriatal pathway projects from the substantia nigra pars compacta to the dorsal striatum and has a prominent role in motor planning and executive movement. The mesocortical pathway arises from the VTA and projects to the temporal and frontal cortices. It is believed to be important in concentration, working memory and executive functioning. The mesolimbic pathway also arises from the VTA, but unlike the nigrostriatal pathway the mesolimbic pathway projects to the ventral striatum, hippocampus, amygdala and septum. The mesolimbic pathway has been associated with motivation and pleasure sensation (Dunlop & Nemeroff, 2007).

Besides the aforementioned dopaminergic pathways, there are also the tuberoinfundibular tract, the incertohypothalamic pathway as well as the projections that are associated with the thalamus. The tuberoinfundibular tract arises from the arcuate nucleus of the hypothalamus and it projects to the median eminence of the hypothalamus,

where it regulates some hypothalamic and pituitary peptides such as prolactin (Kaplan et al., 1994). The incertohypothalamic pathway originates from the cell bodies in the medial portion of the zona incerta and projects to the amygdala and the hypothalamus. It is involved in sexual behavior and arousal. Finally, recent research has shown that there is significant innervation of the thalamus via dopaminergic pathways (please see Figure 9 below). These pathways originate from multiple sites and include the periaqueductal gray matter, the ventral mesencephalon, hypothalamic nuclei, and the lateral parabrachial nucleus. Although the full function of these pathways are not known, it is believed that they contribute to the gating of information that is transferred through the thalamus via the amygdala, striatum and the neocortex (Dunlop & Nemeroff, 2007).

Regarding dementia, in vivo research with AD has demonstrated that the uptake of the D_1, but not the D_2 receptor is reduced in the putamen and caudate nucleus (Kemppainen, Ruottinen, Nagren, & Rinne, 2000). On the other hand, D_2 receptors in both the left and right hippocampus are reduced when compared to controls and such reductions have been correlated with memory and attention impairments (Kemppainen, Laine, Laakso, Kaasinen, Nagren, Vahlberg, et al., 2003). Furthermore, individuals with DLB and AD when compared to persons with just AD demonstrate increased D_1 receptor density and decreased D_2 and D_3 receptor density. In this manner, the D_3 receptor has been implicated in the pathogenesis of psychosis (Sweet, Hamilton, Healy, Wisniewski, Henteleff, Pollock, et al., 2001). Research on the concentrations of DA and it metabolites indicates that for individuals with AD there are reduced levels of DA in the nucleus amygdalae, substantia nigra, grays cinguli, and the raphe system (Storga, Vrecko, Birkmayer, & Reibnegger, 1996). For persons with FTD, SPECT studies have shown

significantly decreased presynaptic dopaminergic nerve terminals and mild reduction of postsynaptic D_2 receptor binding in the striatum. Similarly, research by Huey et al. (2006) have reported decreased levels of HVA and DA in the CSF of persons with FTD, while Court & Perry (2003) indicate that such reductions are also characteristic of VaD, albeit VaD also show reduced dopaminergic innervation of the caudate nucleus and the striatum.

In regards to the BPSD, dopaminergic deficits have been associated with wandering (Meguro et al., 2004), depression, apathy, anxiety (Dunlop & Nemeroff, 2007), aggression and psychosis (Holmes, Smith, Ganderton, Arranz, Collier, Powell, et al., 2001). For persons with depression and anxiety the research suggests that anxiety is related to decreased D_2 receptor expression, while depression has been related to reduced dopamine transporter (DAT) density and elevated D_2/D_3 receptor binding in the central and basal nuclei of the amygdala (Dunlop & Nemeroff, 2007). For persons that demonstrated physical aggression and psychosis, research by Holmes et al. (2001) indicates that physical aggression is associated with the D_1 receptor, whereas psychosis is associated with the D_3 receptor.

For individuals who wander, the research suggests that there is a decrease the metabolism of glucose in the frontotemporal region as well as decreased metabolism of DA in the striatum (Meguro et al., 2004). In light of these findings, some researchers have proposed that the frontostriatal circuit (i.e., this circuit regulates the functioning between the frontal cortices and the striatum) is involved in wandering behavior and that the underlying neural mechanism is likely reduced activation of the neocortex (Meguro et al., 2004). On the basis of this assumption, Meguro et al. (2004) examined the efficacy of

Figure 9: Illustration depicting dopaminergic neural pathways in the human brain

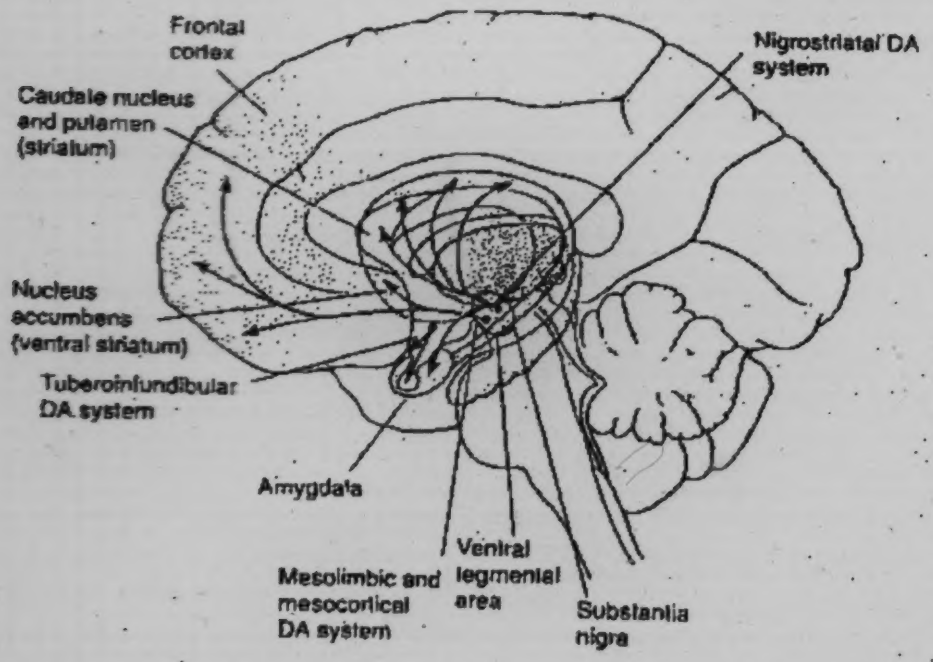

Figure Caption: Figure depicting the dopaminergic noradrenergic pathways of the human brain. The axons of the central dopaminergic system originate in the retro-rubro field, the substantia nigra pars compacta and the ventral tegmental area (VTA). From here, the axons project along three different pathways via the medial forebrain bundle to innervate specific cortical and subcortical structures. These include the mesolimbic, mesocortical and the nigrostriatal pathways. The nigrostriatal pathway projects from the substantia nigra pars compacta to the dorsal striatum. The mesocortical pathway arises from the VTA and projects to the temporal and frontal cortices. It is believed to be important in concentration, working memory and executive functioning. The mesolimbic pathway also arises from the VTA, but unlike the nigrostriatal pathway the mesolimbic pathway projects to the ventral striatum, hippocampus, amygdala and septum. The tuberoinfundibular tract arises from the arcuate nucleus of the hypothalamus and it projects to the median eminence of the hypothalamus, where it regulates some hypothalamic and pituitary peptides such as prolactin. The incertohypothalamic pathway originates from the cell bodies in the medial portion of the zona incerta and projects to the amygdala and the hypothalamus. Taken from http://www.benbest.com/science/anatmind/FigX16.gif on February 4, 2008

risperidone as a treatment for patients that exhibited wandering behavior. The authors concluded that risperidone was effective for reducing the wandering behavior, but that the observed reduction was not due to D_2 receptor blockade. Instead, the authors proposed that the observed reduction in wandering behavior was the result of 5-HT_{2A} antagonism in the neocortex, whereby blocking 5-HT_{2A} receptors produced the physiological arousal that is necessary to stimulate the neocortex. With increased stimulation, the neocortex's level of activity is comparable to the demands of the environment and on the basis of this similarity the person with dementia is less agitated and therefore less likely to demonstrate wandering behavior (Meguro et al., 2004). This interpretation seems plausible, as previous research by Stewart (2001) indicates that dopaminergic stimulation with methylphenidate is effective for some people that experience rest-activity disorders.

Gamma-Aminobutyric Acid (GABA)

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the CNS. It is synthesized from glutamate by the enzyme glutamic acid decarboxylase (GAD) and is metabolized into succinic acid semi-aldehyde by the enzyme GABA-transminase (GABA-T) (Lanctôt, Herrmann, Rothenburg, & Eryavec, 2007). In nature, glutamate is found in foods such as diary products, meats, nuts and legumes (Kaplan et al., 1994).

To date, three subtypes of the GABAergic receptors have been identified, $GABA_A$, $GABA_B$ and $GABA_C$. Both the $GABA_A$ and $GABA_B$ receptors are located within the CNS, while $GABA_C$ is found in the retina. The $GABA_A$ receptor is found both pre- and postsynaptically and is more widely distributed than $GABA_B$. It is intricately interconnected with other neurons and it functions in many cases as a neuromodulator.

For example, when the $GABA_A$ receptor is activated by an agonist it will cause the cell to become hyperpolarized and in doing so, it can reduce the synaptic transmission of 5-HT, DA and ACh (Lanctôt, Herrmann, Rothenburg, & Eryavec, 2007). Alternatively, preliminary investigations have demonstrated that unlike the $GABA_A$ receptor, $GABA_B$ does not respond to benzodiazepines, barbiturates or steroids. Pharmacologically, postsynaptic activation of $GABA_B$ reduces neuronal excitability in the hippocampus, while presynaptic activation has been shown to inhibit the release of glutamate. Medications that inhibit the release of glutamate (i.e., Memantine, Ebixa®) reduce neuronal excitation and thereby decrease excitotoxicity (Lanctôt, Herrmann, Rothenburg, & Eryavec, 2007). The latter is an important finding, as slowing the process of excitotoxicity has been associated with improved behavioral presentation and the slowing of cognitive impairment (Herrmann & Lanctôt, 2007).

There are three lines of evidence that support the possibility of GABAergic disruption in AD and the other dementias. These include postmortem studies, neuroimaging studies and markers of CNS GABA. Collectively, postmortem research has shown that individuals with AD may have reduced concentrations of GABA in the frontal, temporal and parietal regions, while research on people with FTD suggest that their GABAergic system is relatively intact (Huey et al., 2006). For persons with AD, reductions in GABA have also been found in the limbic system, cingulate, amygdala and the thalamus, while GABA levels in the hippocampus, caudate, putamen and nucleus accumbens appear unaffected (Lanctôt, Herrmann, Mazzotta, Khan, & Ingber, 2004). Neuroimaging studies have shown similar results as postmortem studies and the research

on the markers of CNS GABA in patients with AD have found significant reductions in the CSF (Lanctôt, Herrmann, Rothenburg, & Eryavec, 2007).

To date, the role of GABA in dementia and the BPSD remains unclear. The research has supported a link with depression and apathy but others associations to the BPSD have not been established. Having said that, the research has indicated that GABA provides significant regulatory control over serotonergic and dopaminergic neurons that control aggression, psychosis, mood and cognition. In this fashion and after considering that GABA is a primary CNS inhibitory neurotransmitter, it is likely that the full role of GABA's involvement in the pathology of the BPSD has yet to be discovered (Lanctôt, Herrmann, Rothenburg, & Eryavec, 2007).

Acetylcholine (ACh)

Acetylcholine or 2-acetoxy-N, N, N-trimethylethanaminium (ACh) is an ester of acetic acid and choline that acts as an excitatory neurotransmitter in both the CNS and PNS. It is critical for memory function and cognition. Both acetic acid and choline are obtained from the diet and are typically found in foods such as eggs, beef liver, broccoli and nuts. Once it is ingested, choline crosses the blood brain barrier where it is synthesized with Acetyl-CoA by choline acetyltransferase (ChAT) to form ACh (Kaplan et al., 1994). Unbound ACh exists in the intracellular and extracellular spaces where it is degraded by the cholinesterases, a family of cholinergic enzymes that act centrally and peripherally to maintain normal cholinergic functioning. In regards to AD, the two most important cholinesterases are AChE and BuChE. AChE acts primarily in the CNS, while BuChE plays a more active role at peripheral sites such as the liver, gastrointestinal tract and plasma (Rivas-Vasquez, 2001).

In terms of neurotransmission, cholinergic neurons arise in the basalis of Meynert (BMN) and the pedunculopontine nucleus (PPN). The BMN innervates the cortex, thalamus, hippocampus and a variety of subcortical structures, while the PPN projects to the midbrain and the thalamus. The PPN pathway is involved in the sleep-wake cycle and is important for conscious awareness (Lanari et al., 2006). The projections of the BMN are associated with learning and memory and are involved in the cognitive integration of trivial and motivationally relevant information (please refer to Figure 10 given below). Within these systems there are two main types of cholinergic receptors, muscarinic and nicotinic, of which both are widely distributed throughout the brain. In certain regions of the brain only the muscarinic subtype is found (i.e., the midbrain, medulla, and pons), while in other regions (i.e., the substantia nigra, locus coeruleus and septum) only the nicotinic receptor subtype is found. Both sub-types are found in the corpus striatum, cerebral cortex, hippocampus, thalamus, hypothalamus and cerebellum. Muscarinic receptors are further classified as M_1–M_5, and nicotinic as N_N and N_M (Mesulam, 2004).

For people with FTD the research indicates that their cholinergic system is relatively intact (Huey et al., 2006) while for people with AD, DLB and VaD the research suggests that they experience significant cholinergic abnormalities (Minger, Esiri, McDonald, DPhil, Carter, Hope, et al., 2006; Ballard et al., 2006; Roman & Kalaria, 2005). For example, Hanyu, Shimizu, Tanaka, Hirao, Iwamoto, & Abe (2005) examined the thickness of the substantia innominata of patients with AD, DLB and VaD and found that all the dementias demonstrated atrophy in this area, albeit atrophy was the greatest for the patients diagnosed with DLB. It was further noted that after 12-weeks of

donepezil treatment the thickness of the substantia innominata in participant's with AD and DLB was inversely and significantly correlated to cognitive performance, whereas no

Figure 10: Illustration depicting cholinergic neural pathways in the human brain

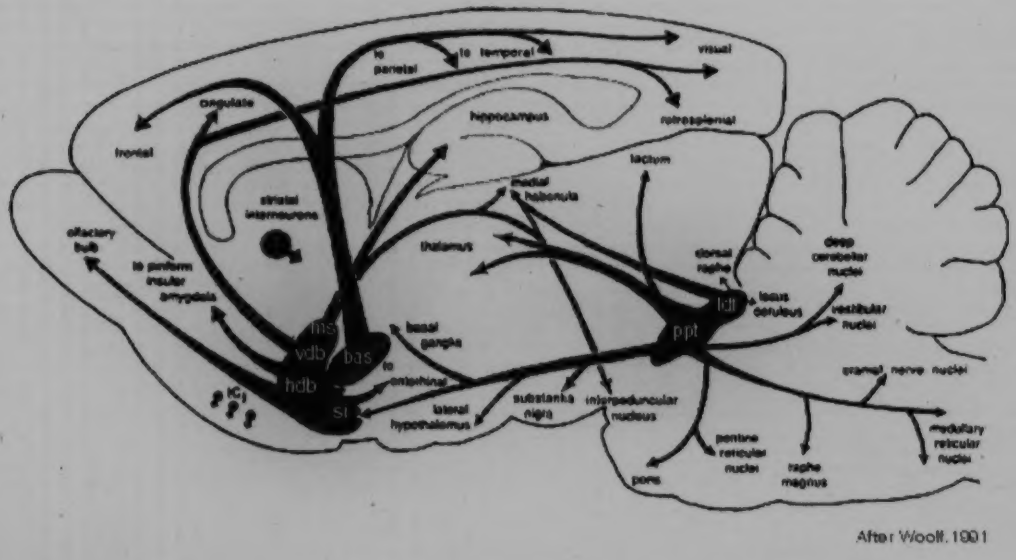

Figure Caption: Figure depicting the cholinergic pathways of the human brain. Cholinergic neurons arise in the basalis of Meynert (BMN), which contain nucleus basalis, substantia innominata and horizontal diagonal band: bas, si, hdb that project cholinergic axons to all parts of the neocortex, parts of limbic cortex and to the amygdala. The cholinergic pontomesencephalon neurons (laterodorsal tegmental and pedunculopontine tegmental nuclei: ldt and ppt) project onto hindbrain, thalamus, hypothalamus and basal forebrain. Taken from http://www.albion.edu/psychology/fac_psyc/jwilson/nspharm/CholinergicFigurewoolf.GIF on November 16, 2007

correlation was found for VaD. These findings suggest that persons with VaD may demonstrate different cholinergic neuro-degeneration than those with other types of dementia and that the observed differences in ChEI therapy may partly be attributable to differences in cholinergic neuropathology (Hanyu et al., 2005).

In addition to the above, the thalamus receives cholinergic input from the BMN and the PPN and is an essential component in the cortico-basal ganglia-thalamocortical circuits. In fact, thalamic-cholinergic activity has been implicated to play a major role in modulating cortical activity as well as behavioral disturbances. For example, the mediodorsal (MD) thalamic nuclei project to key frontal circuits (i.e., the cingulate) and are involved in cognitive and psychiatric symptoms. Efferents from the centromedian thalamic nuclei (CM) project to the motor cortex and are believed to be involved in the motor abnormalities that are observed in dementia, while the reticular (Re) thalamic nuclei control other thalamic nuclei via projections from the dorsal thalamus (Ziabreva et al., 2006).

For individuals with dementia the research has suggested that the functionality of these nuclei is impaired and that such deficits can be indicative of a person's type of dementia. For example, research by Ziabreva et al. (2006) has demonstrated that the presence of Parkinsonism (P) in persons with DLB is related to a significant increase in the ChAT activity of CM thalamic nuclei. Alternatively, for persons with PDD, there is significantly lower thalamic activity than controls in the Re and MD thalamic nuclei, which suggests that significant presynaptic cholinergic deficits occur only in conditions where both cortical and subcortical neurodegeneration is evident (Ziabreva et al., 2006).

The research into the cholinergic deficits of dementia has also demonstrated that there are significant reductions in ChAT activity and that such reductions are associated with severity of cognitive impairment (Di Lazzaro, Pilato, Dileone, Saturno, Oliviero, Marra, et al., 2006). Furthermore, for individuals with AD there are significant disruptions to the efferent cortical cholinergic neurons of the BMN and that these

disruptions have been linked to memory problems and the ability to learn new information. The later is likely a result of lesions and/or neuritic plaques that in effect disconnect the link between the BMN, the neocortex and the hippocampus (Lanari et al., 2006).

To date, the relationship between cholinergic abnormalities and dementia has mostly been its relationship to cognitive impairment (Steur & Wevers, 2002). However, there is a growing body of evidence to suggest that ACh's involvement with the BPSD is more than just its effect on cognition. For example, the research suggests that cholinergic deficits can contribute to aggression, psychosis and depression (Lanari et al., 2006) as well as sundowning behavior (Staedt & Stoppe, 2005). For example, in persons with AD, the suprachiasmic nucleus (SCN) receives less cholinergic input from the BMN and this has been shown to lead to alterations of circadian rhythms as well as the ability to perceive external Zietgebers. According to Staedt & Stoppe (2005) "…sundowning is pathophysiologically based on a cortical activation (arousal stimuli) with concurrently reduced indirect SCN-medicated based activation which is additionally enhanced by the cholinergic deafferentiation of the cortex and reduced cholinergic inhibition of the nuclei reticulares thalami". In effect, the person with AD is in a state of arousal but the neocortex is "turned off" and telling the brain to initiate NONREM sleep. Accordingly, the person with AD is unable to build up the attentional capacity that is necessary to process the stimulation from their environment. As a result, their agitation persists and in most cases is displayed as increased wandering, fidgeting and motor-restlessness. In other cases, such agitation can be displayed as vocally disruptive behavior (Staedt & Stoppe, 2005).

Continuing with the above, the research indicates that the ChEIs have pharmacological properties that are able to reduce the severity of the BPSD seen in AD (Finkel, 2004) and that these agents exert their effect on the frontal and temporal structures that mediate emotional behaviors (Lanari et al., 2006). For example, cholinergic abnormalities in AD are routinely noted in the temporal and frontal lobes and research indicates that fronto-temporal structures and the amygdala are implicated in the pathogenesis of psychosis, apathy and emotional indifference. As with learning and memory, the pathogenesis of these behaviors is believed to be a result of lesions and/or neuritic plaques that in effect chemically disconnects the link between the BMN, the neocortex and the limbic system (Lanari et al., 2006). Accordingly, by administering a ChEI there is an increase in the synaptic concentrations of ACh and with ACh more available the efficiency of the neurotransmission between the BMN, neocortex and the limbic system is improved (Lanari et al., 2006; Rivas-Vazquez, 2001).

In summary, the research has shown that there are significant cholinergic deficits in persons with DLB, AD, VaD, but that the cholinergic system of a person with FTD is relatively intact. Furthermore, the cholinergic system represents the most important neuromodulatory neurotransmitter system in the brain and there is continued evidence to suggest that ACh is primarily involved in the pathogenesis of the cognitive symptomology of AD. Having said that, the research does support ACh's involvement in other BPSD (i.e., aggression, apathy, and depression) and considering that ACh is one of the primary excitatory neurotransmitters it is likely that the full role of ACh's involvement has yet to be discovered (Herrmann & Lanctôt, 2007).

Based on the above, the BPSD can arise from brain atrophy, alterations to neural circuitry, deficits to the concentrations of specific neurotransmitters as well as dysfunctional neurotransmitter systems. Of these possibilities, deficits to the concentrations of specific neurotransmitters and dysfunctional neurotransmitter systems are the most amenable to human intervention. To date, ACh, 5-HT, NE, DA and GABA have been the most studied, but the literature suggests that more research is needed. In addition, the neurotransmitters discussed above account for only part of the numerous neurochemical possibilities that might underlie the presentation of the BPSD. There are numerous neuro-chemicals, neuro-peptides and proteins that can act as chemical messengers (Herrmann, 2001) and as more research is conducted it is likely that our knowledge of the BPSD will improve considerably.

Having provided a review of the neural circuitry of human vocalisation and an examination of the neurotransmitter deficits of dementia, the author will now propose a neurological/cognitive model that could possibly underlie the presentation of VDB.

Neurological/Cognitive Model

According to the proposed model, VDB develops as a result of specific alterations (i.e., neurochemical and/or neuroanatomical) to the pathways and anatomical brain areas that interconnect the cerebral cortex, the mediofrontal cortex, the basal ganglia, the cerebellum, and the PAG with the phonatory motoneurons. These changes are believed to occur as a progressive process (albeit simultaneous dysfunction is also possible) whereby alteration to the voluntary speech structures (i.e., the substructures of the basal ganglia and/or the cerebellum) would occur first and be followed by neuronal dysfunction of the neuroanatomical areas that facilitate involuntary speech (i.e., the PAG). With time and as

the illness progresses, the voluntary control over the substructures of the basal ganglia and the cerebellum would deteriorate and in doing so the cerebral cortex and the mediofrontal cortex would no longer be capable of generating and/or relaying appropriate neural messages to the phonatory motoneurons. At this point in the illness, most, if not all vocalization would be the result of involuntary (i.e., visceromotor) speech that is facilitated by the PAG. As the individual continues to deteriorate it is assumed that the PAG will also experience neuronal dysfunction (i.e., atrophy or neuronal changes secondary to an ischemic event) and that as a result there will be specific alterations to the initiation and/or control of involuntary speech (Schultz et al., 2005).

Based on the above information, the proposed model suggests that during the course of pathological brain atrophy, talking-VDB (i.e., those that repeat the same word) would develop first and be followed by muttering-VDB (i.e., mostly uttering unintelligible words), singing-VDB, and lastly by screaming-VDB (i.e., mostly uttering nonsensical noises at loud volumes). In this manner, talking-VDB would exhibit the most control over the ability to speak, whereas a person that exhibits screaming-VDB would have no and/or minimal control. As such, the proposed model contends that the person who mutters and/or sings would be characterized by neuronal deterioration that is more severe than talking-VDB but less severe than a person who exhibits screaming-VDB.

Due to the complexity of VDB's pathology, it is important to note that the proposed model has not considered muttering-VDB and singing-VDB as individual pathologies. Instead, this model assumes that both conditions are a more dysfunctional version of talking-VDB that has resulted from the progressive deterioration of the neuronal circuitry. As to singing-VDB, the model has also assumed that in addition to the

neuronal deterioration of talking-VDB, this presentation would also experience a significant alteration and/or dysfunction in the right hemisphere as well as the anatomical brain areas that function in the formation and retrieval of memory (i.e., the hippocampus). Due to this level of complexity, singing-VDB is not explicitly explained and/or discussed by this model, but it is assumed, as mentioned above to involve the deterioration of the neural circuitry that has been proposed for talking-VDB.

According to the proposed model, the neural pathways and associated structures that control voluntary speech would deteriorate and/or experience neuronal dysfunction first and be followed by deterioration and/or neuronal dysfunction to the neural pathways and associated structures that are associated with involuntary speech. In this manner, the proposed model has suggested that talking-VDB would present before screaming-VDB. As such, it is likely that the pathology of talking–VDB is not the result of the person's inability to perceive a specific stimulus and/or generate a motor response, albeit it is possible that some dysfunction is present. Instead, it would appear that the problem resides with the ability to stop talking once the person has started. For example, a person could respond to the question, "How are you today" with "I am fine or fine". Once they have finished their statement they are unable to stop talking and as a result they continue to repeat the same word. Similar situations may arise from other sensory stimuli (i.e., visual, auditory, tactile, or olfactory) whereby a certain stimulus may illicit vocalization. For example, a person may see an altercation across the dining room and start repetitively calling out for help, and continue to call out even after the altercation has been brought under control.

Referring to Figure 4, it would appear that one possible neurological explanation for talking-VDB is that there is an alteration (i.e., neurochemical or neuro anatomical) to the diverse neural circuitry that interconnects the substructures of the basal ganglia with the mediofrontal cortex. In general, cortical activity that excites the striatum participates in the direct pathway and releases the inhibition of the globus pallidus interna and the substantia nigra. By releasing the inhibition of the globus pallidus interna and the substantia nigra, cortical excitation releases the tonic inhibition of the thalamus (i.e., equivalent to releasing the brake). Alternatively, cortical cells that excite the striatum in the indirect pathway are believed to act through the globus pallidus externa and the nucleus subthalamicus to disinhibit the globus pallidus interna and the substantia nigra. In turn, these processes inhibit the disinhibition (i.e., equivalent to applying the brake) of the thalamus (Amos, 2000). In this manner, the repetitive uttering of the same word (i.e., fine, fine, etc) is possibly explained by a failure of the basal ganglia to disinhibit the thalamus, whereby the neural message from the thalamus continues to excite the cerebral and mediofrontal cortexes. Through this process the mediofrontal and cerebral cortexes would continue to send excitatory input to the basal ganglia, the phonatory motoneurons and the cerebellum, which according to the proposed model could present as talking-VDB. Please see Figure 11 for an illustration of the substructures of the basal ganglia as well as its associated neurotransmitters.

Again referring to Figure 4, a second possibility for the occurrence of talking-VDB involves the diverse interconnections of the cerebellum and/or the pathways and anatomical brain areas that connect these areas (i.e., the thalamus, pons and the medulla oblongata) to the phonatory motoneurons. As stated above, the cerebellum sends

excitatory information to the cerebral cortex via the thalamus along the cerebellothalamocortical pathway and from the cerebral cortex neural messages are sent to the cerebellum via the pons along the corticopontocerebellar pathway. In regards to talking-VDB it is possible that the cerebellum is overactive (i.e., due to excessive noradrenergic activation from the LC (see Grijalba, Berciano, Anciones, Pazos, Pascual, 1994) and that when an individual vocalizes, the cerebellum is unable to modulate the person's vocalization. In this manner, the excessive excitatory output from the cerebellum continues to excite the cerebral cortex, which in turn causes the cerebral and mediofrontal cortexes to send excitatory input back to the cerebellum as well as the phonatory motoneurons. The continued excitatory neural input to the phonatory motoneurons could result in continued vocalization or possibly some alteration of normal speech that is characteristic of talking-VBD.

The cerebellum modulates the profile, intensity and the duration of movements according to the circumstances in which the movements occur, as signaled by visual, auditory, somatosensory, and vestibular inputs. In this regard, some researchers have proposed that cerebellar dysfunction is a likely candidate for explaining conditions such as PLC whereby such behavioral presentations arise from lesions to the corticopontocerebellar pathway. In this manner, it has been proposed that the structures of the cerebellum are operating on the basis of corrupt information and that as a result it produces specific behavioural presentations in response to specific external stimuli (Parvizi et al., 2001). In this regard, it is possible that within the broader context of dementia's pathology a similar neural mechanism is occurring in persons that display talking-VDB and that because of this future research will be needed to clarify the nature

of VDB's neural pathology.

It has been proposed that VDB results from a progressive disconnection between the cerebral cortex, the mediofrontal cortex and its connections to the phonatory motoneurons. For the individuals that exhibit screaming-VDB, the model suggests that

Figure 11. Illustration of the basal ganglia and its associated neurotransmitters

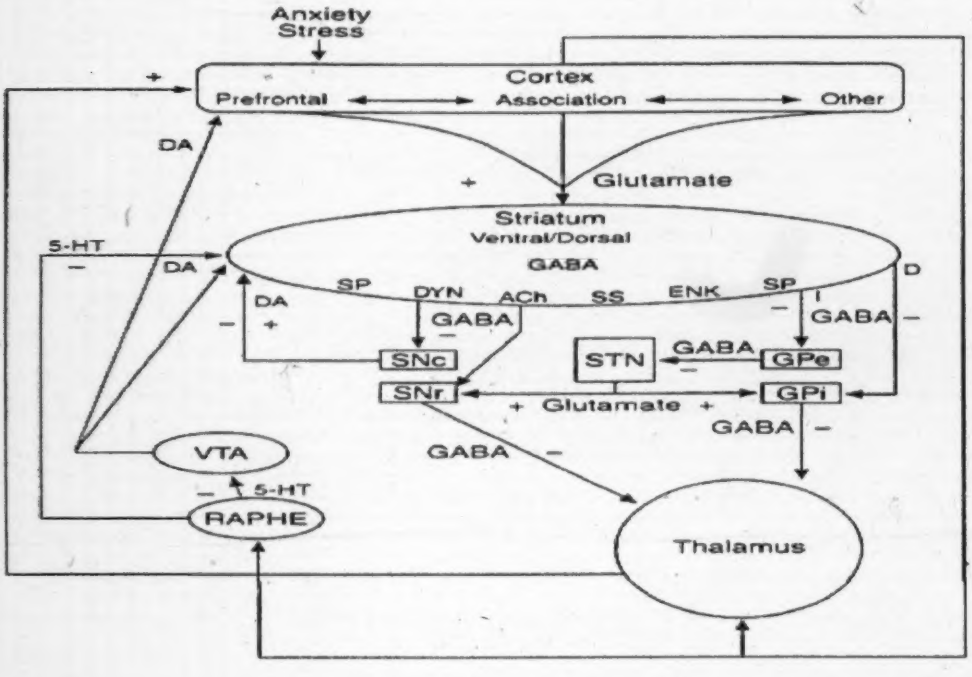

Figure Caption: Figure depicting a model for agitation as it relates to different Neurotransmitters and neural pathways. Abbreviations: 5-HT = serotonin, ACh = Acetylcholine, D = direct pathway, DA = dopamine, DYN = dynorphin, ENK = Enkephalin, GABA = y-aminobutyric acid, GPe = global pallidus externa. GPi = global pallidus interna, I = indirect pathway, RAPHE = median raphe nuclei. SNc = substantia nigra pars compacta, SNr = substantia nigra pars riticulata, SP = substance P, SS = somatostatin, STN = subthalamic nucleus, VTA = ventral-tegmental area. Symbols: + = Excitatory. - = Inhibitory. Reprinted from Lindenmayer, J. (2000). The Pathophysiology of agitation. *Journal of Clinical Psychiatry, 61*(Suppl14), 5-10.

these individuals experience significant alteration and/or dysfunction in the anatomical brain areas that control voluntary speech that has been further complicated by dysfunction and/or deterioration in the structures of the brain that control involuntary speech. In this manner, the proposed model has assumed that there is an alteration (i.e., neuroanatomical and/or neurochemical) in the descending pathway that connects the mediofrontal cortex with the PAG and the motoneurons in the pons, medulla, and the ventral horn of the spinal cord (Jűrgens, 2002). Accordingly, the abnormal control of voluntary speech that is characteristic of talking-VDB would not necessarily be present in a person that displays screaming-VDB (albeit some residual control and/or neuronal connectivity is possible), instead, all monitoring of the phonatory motoneurons and/or initiation of vocalization would be facilitated by the PAG.

The PAG of the midbrain rapine represents one of the oldest structures that is involved in vocalization. It is believed to represent an evolutionary link to non-human primates, and to function as a vocal trigger for emotional and motivational sensory input (Esposito et al., 1999; Dujardin & Jűrgens, 2006). As a structure of the midbrain, the PAG receives afferent projections from the midline thalamus, mediobasal amygdala, hypothalamic nuclei and the anterior cingulate cortex. It sends efferent projections to the reticular formation of the pons and medulla where it controls laryngeal, respiratory and supralaryngeal activities (Jűrgens 2002). According to Schultz et al. (2005) the PAG is activated during the vocalization of voluntary and visceromotor speech but is inactive when humans are "thinking" about what it is that they want to say. In other words, when humans formulate voluntary speech the mediofrontal cortex will only send neural messages to the basal ganglia and the cerebellum (i.e., presumably to prevent these

structures from innervating the reticular formation) and that it does not innervate the PAG until the individual begins to speak. In this regard, the research would suggest that the PAG represents a final pathway for all vocalization that is involved in both voluntary and involuntary speech (Schultz et al., 2005).

Referring to Figure 12, one can see that the pathway that connects the PAG to the mediofrontal cortex is separate from the basal ganglia and the cerebellum but that each structure terminates onto the reticular formation. Based on this structural layout and after considering that the PAG is activated during voluntary and involuntary speech, there are several possible explanations that may account for the repetitive screaming and/or moaning like behavior that is characteristic of screaming-VDB. Previous research has established that the PAG of the midbrain rapine is also affected by neuritic plaques and tangles, and that such morphological changes significantly interrupts its normal cellular functioning (Parvizi, 2000). Accordingly, the proposed model would suggest that screaming-VDB is the result of no and/or limited control over the substructures of the basal ganglia and cerebellum that has been further complicated by significant cellular alterations to the PAG. Although the exact neurological mechanism is not known, excitation of the PAG would appear to be a reasonable explanation for the presentation of screaming like behavior. In this regard, excitation of the PAG would be presumed to occur as a result of corrupt neural messages from the mediofrontal cortex or as a result of some pathological alteration that has prevented the PAG from generating and/or relaying the appropriate motor output to the reticular formation. Accordingly, by operating on the basis of corrupt and/or incomplete information the PAG would send inappropriate

information to the reticular formation, which would arguably result in the continued and/or erratic vocalization.

Having provided the above, it is important to note that the actual underlying cause of VDB is not known. However, after considering the aforementioned areas involvement in other conditions that display aberrant vocalizations it is reasonable to suggest that the proposed model has some validity for explaining the pathology of VDB. Knowing this, it is still probable that some individuals will develop VDB through a process that is different from that proposed by this model. For example, some individuals will not develop screaming-VDB even though they displayed talking-VDB. Furthermore, it is also possible that talking-VDB and screaming-VDB could co-exist whereby an individual could demonstrate both conditions simultaneously or at different times throughout the day. In this regard as well as for other possibilities not discussed here, it is likely that such manifestations are the result of specific pathological characteristics that have occurred within specific areas of the vocalization network discussed above. For example, in a situation where a person displays screaming-VDB but not talking-VDB, it is quite likely that the person had an ischemic event or other pathological characteristic that enabled the development of the specific VDB presentation. Having said that, it is important to note that even though some people may not develop VDB as proposed by this model, it is reasonable to assume that for many cases of VDB the underlying pathology will occur as a result of some dysfunction to the aforementioned anatomical areas.

After reviewing the information from above and after considering that all dementias experienced progressive deterioration of the cortical areas, it would appear that any of the

Figure 12: Figure outlining neural circuitry that connects both voluntary and involuntary speech to the phonatory motoneurons

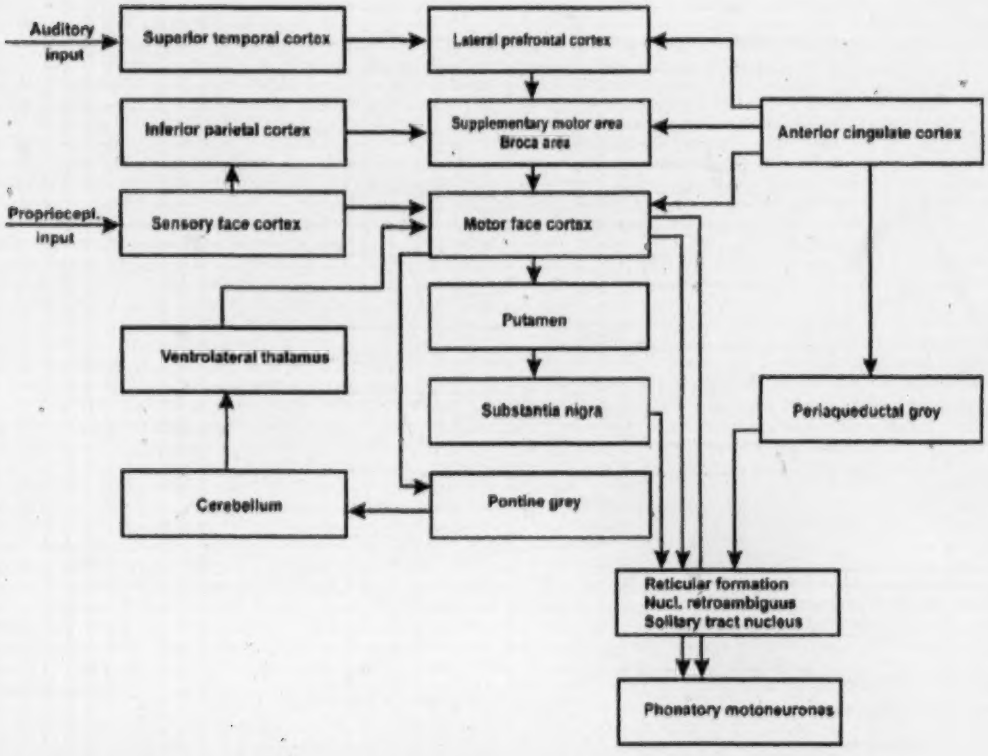

Figure Caption: In the figure, the anterior cingulate cortex (i.e., mediofrontal cortex) innervates the periaqueductal grey (PAG) and from the PAG neural information (i.e., motor) is sent to the reticular formation and unto the phonatory motoneurons. Please note that the PAG is associated with visceromotor (i.e., involuntary speech) and that it adds the emotional content to voluntary speech as inputted from the mediofrontal cortex. Also note that Broca's area (i.e., the site where voluntary motor commands for speech are generated) innervates the facial motor cortex, which innervates the reticular formation and from the reticular formation neural messages are sent to the phonatory motoneurons. Also note the cerebellum's pathway through the ventral thalamus to the facial motor cortex as well as the substructures of the basal ganglia (i.e., substantia nigra and putamen) connections to the reticular formation and unto the phonatory motoneurons. Reprinted from Jürgens, U. (2002). Neural pathways underlying vocal control. *Neuroscience & Biobehavioral Reviews,* *26*(2), 235-258.

discussed dementias could develop VDB. Furthermore, since VDB appears to be associated with cortical atrophy/neuronal degeneration and since these processes are associated with cognitive impairment it is likely that the latter is one explanation as to why screaming-VDB is usually associated with those that are severely demented (see Kopala & Honer, 1997). Furthermore, it has been my own clinical experience that screaming-VDB is most often displayed by individuals that cannot ambulate (i.e., independently, with nursing staff assistance or via a wheelchair) or maintain their posture when placed in a sitting position. In this regard, the loss of the cerebrum's control over the basal ganglia and the cerebellum seems reasonable, as both of these structures are responsible for body posture as well as the ability to walk. However, it is important to note that these individuals still posses some neurological connection between the cerebral cortex, the mediofrontal cortex, the basal ganglia and the cerebellum and as a result it is possible that cerebellar and basal ganglia dysfunction is also involved with screaming-VDB. For example, even though these individuals cannot walk, maintain their posture or control their ability to speak, they can still open their mouth when presented with food and most, although weak can still chew and/or swallow.

In the following section, the pathology of each of the dementias will be revisited, and by way of anatomical and neurochemical deficits, an explanation of how each condition could develop VDB will be presented. In AD, the neurofibrillary tangles and neuritic plaques that are typical of this disease generally affect the locus coeruleus, hippocampus, midbrain rapine, amygdala, superior temporal cortex, inferior parietal cortex, and the PAG (Herrmann et al., 2004; Rivas-Vazquez, 2001; Parvizi, 2000). Sometimes the whole brain is affected (Parvizi, 2000). By referring to the model given

above, it would appear that the pathology of AD is conducive to developing VDB and in this regard one would expect that VDB pathology would be the more prevalent in persons diagnosed with AD. The latter would appear to be especially true for the presentations of screaming-VDB. For persons with VaD, ischemic changes and other cerebrovascular events are possible in any part of the brain and the probability of developing VDB would be directly related to the areas of the brain that are most affected. For example, if the nuclei of the ventrolateral thalamus are inhibited and/or destroyed (i.e., ischemic event) vocal control is severely impaired and in such cases, vocalizations can become breathy, jittery and monotonous (Jűrgens, 2002). Similarly, for people with DLB the formation of lewy bodies are characteristic of the subcortical areas of the brain as well as the brainstem, archicortical and neocortical areas (Ziabreva et al., 2006; Ballard et al., 2006), which as mentioned above are involved in the vocalization network. Individuals with FTD are characterized by the presence of ubiquitin-positive, tau α-synuclein – negative intracellular inclusions within the frontal and temporal cortices, as well as the dentate gyrus of the hippocampus. These structures are involved in planning, higher-order cognitive functions and memory, which are processes that are necessary for voluntary speech (see Whitwell et al., 2005; Schultz et al., 2005).

As mentioned above the cerebellum serves an excitatory function whereas the basal ganglia serve an inhibitory function. In regards to the neurochemical messaging, research suggests that the basal ganglia utilize GABA, Glu, ACh and DA as its primary neurotransmitters, albeit neuro-peptides and 5-HT are also used. ACh and Glu are excitatory, GABA is inhibitory and DA serves a modulating effect, whereby (i.e., either the direct or indirect pathway) it can provide an inhibitory or excitatory effect. For

example, the striatum produces inhibitory effect on the globus pallidus interna and externa as well as the substantia nigra pars reticulata via GABAergic input. The globus pallidus externa uses GABA to inhibit the subthalamic nuclei, while the globus pallidus internal inhibits the thalamus. Alternatively, Glu is used by the subthalamic nuclei to provide excitatory input to the globus pallidus interna as well as the substantia nigra pars reticulata. Glu is also used by the thalamus to excite the cortex and the cortex uses Glu to excite the striatum (Amos, 2000). The striatum also receives dopaminergic input from the substantia nigra pars compacta, the ventral tegmental area (VTA), and serotonergic input from the dorsal raphe nuclei (Lindenmayer, 2000).

In regards to its specific neural pathways, there are three main pathways that provide input and output to and from the cerebellum. The three afferent pathways arise from the spinocerebellar tract (i.e., mossy fibers), the inferior olive (i.e., climbing fibers), and the pons (i.e., mossy fibers). Axons coming from the cerebral cortex synapse onto the pons (i.e., corticopontine) and from the pons they crossover and enter the cerebellum as mossy fibers. Mossy fibers from spinocerebellar tract provide proprioceptive input, while climbing fibers from the inferior olive are contralateral and are important for vestibular control and balance. Efferent projections from the cerebellum arise from the deep nuclei (i.e., the fastigial, interposed and dentate nuclei), where only the dentate nuclei are involved with voluntary speech. These axons project to the thalamus and the red nucleus. As mentioned above the thalamus serves as a relay station for the cerebral cortex and the red nucleus controls muscles in the shoulder and upper arm. In regards to neurochemical messengers, the cerebellum uses 5-HT, DA and ACh as its primary neurotransmitters, as well as histamine, Glu and GABA (see Schweighofer, Doya, Kuroda, 2003).

Research has shown that the PAG is divided into four areas, the dorsal, dorsolateral, ventrolateral and the medial that have been shown to be important for the sensation of pain, autonomic control, vocalization, fear, and anxiety. Within the PAG the major intrinsic neuronal circuit is a tonically active GABAergic network, whereby inhibition is an important mechanism for facilitating the PAG's output. In regards to neurotransmitters and/or chemical messaging, the research has shown that the PAG modulates anxiety and fear responses through serotonergic and GABAergic function. Serotonergic cell bodies are found within the ventrolateral and ventromedial portions of the PAG, whereas both the $GABA_A$ and benzodiazepine receptor have been found throughout the PAG. In this regard, the use of SSRI medications in animal models have been shown to attenuate anxiety, (presumably by serotonergic excitation of GABAergic interneurons) whereas blockade of the $GABA_A$ receptor will increase the PAG's output and in doing so increase aversion like behavior (Sanchez, 2004; Behbehani, 1995).

In regards to vocalization, animal research has shown that electrical stimulation as well as injection of glutamate agonists and GABAergic antagonists can produce vocalization. Electrochemical studies have shown that the dorsolateral portion of the PAG receives extensive connections from the forebrain and acts as a motor coordinator for the phonatory motoneurons. From the dorsolateral region, the PAG sends the phonatory motor commands to the lateral PAG and from here the neural messages are sent to the medulla, the pons, and the ventral horn of the spinal cord. In regards to neurochemical messaging, animal research has shown that the PAG utilizes ACh, Glu, GABA, 5-HT, NE, as well as opioid derivatives. It is also important to note that the same regions of the PAG that control pain are also involved in vocalization. The difference ,

between these two functions is the refractory period for the activation of the analgesic and vocalization pathways, whereby the latency for the analgesic pathway is longer than the latency for the vocalization pathways. In this regard, it would appear that antagonists to GABA and opioids facilitate vocalization, whereas antagonism of NMDA receptors inhibits vocalization. Furthermore, in animal model studies ACh agonists appear to facilitate vocalization, while agonists and antagonists to NE, 5-HT, or DA do not produce any affect on vocalization (Behbehani, 1995). Although, these neurotransmitters are not directly involved in vocalization itself, they are involved in many of the processes (i.e., respiration, phonatory muscle contraction, and tongue movements) that enable vocalization. Accordingly, it is likely that many of the medications that alter these chemical messengers will also have an effect on PAG-facilitated vocalization.

In summary, the proposed model has suggested that VDB exists on a continuum whereby talking-VDB would develop first and be followed by muttering-VDB, singing-VDB, and lastly by screaming-VDB. More specifically, VDB is proposed to develop as a result of specific alterations (i.e., neurochemical and/or neuroanatomical) to the pathways and anatomical brain areas that interconnect the cerebral cortex, the mediofrontal cortex, the basal ganglia, the cerebellum, and the PAG with the phonatory motoneurons. These changes are believed to occur as a progressive process (although simultaneous dysfunction is also possible) whereby alteration to the voluntary speech structures (i.e., the substructures of the basal ganglia and/or the cerebellum) would occur first and be followed by neuronal dysfunction of the neuroanatomical areas that facilitate involuntary speech (i.e., the PAG). Having said that, it is important to note that the actual underlying cause of VDB is not known and that in this regard more research is needed if we are to

understand the underlying neural pathology of this debilitating BPSD. However, after considering the aforementioned areas involvement in other conditions that display aberrant vocalizations it is reasonable to assume that for many cases of VDB the underlying pathology will occur as a result of some dysfunction to the aforementioned anatomical areas.

Research Questions

Research Question 1:

Is there a reported difference in the rating of vocally disruptive behaviour for males versus females?

Null hypothesis 1:

There will be no reported differences in the rating of vocally disruptive behaviour for males versus females.

Research Question 2:

Is there a reported difference in the rating of vocally disruptive behaviour for the participants with different diagnoses?

Null hypothesis 2:

There will be no reported differences in the rating of vocally disruptive behaviour for the participants with different diagnoses.

Research Question 3:

Is there a reported change in the rating of the participant's vocally disruptive behaviour following the introduction of at least one psychotropic medication?

Null hypothesis 3:

There will be no reported change in the frequency of the participant's vocally disruptive behaviour following the introduction of any psychotropic medications.

Delimitations and Limitations

Delimitations

Only the persons who were diagnosed with AD, DLB, VaD, FTD or mixed dementia were included in this sample because these dementias have been the most studied and it was assumed that this knowledge would provide the most insight into the pathology of VDB. Otherwise, this study excluded all persons that scored greater than or equal to 10 on the MMSE during the year prior to their death or discharge. According to Pearsall et al. (1995) MMSE scores ≤ 10 represent a severe level of cognitive impairment, and once an individual has reached this level further cognitive testing is not informative. In this regard, the researcher assumed that if a participant had an MMSE score > 10 they could possibly possess the cognitive abilities to deliberately display VDB (i.e., attention seeking behavior). This type of presentation is considerably different from the presentation of the VDB described above and it is likely that such behavior is performed using neural mechanisms than are not of interest to this study.

Limitations

As with any research design, this study also has limitations. The inclusion criteria that were established for this study are, in part, limiting to the ability to offer generalizations about the larger dementia population. Arguably, if the duration of the study were longer (e.g., 200 days as opposed to 100) and if the sample was larger (e.g.,

100 as opposed to 19) it is likely that the collected data would have provided greater statistical power for generalizing the results. In addition, the data for this study reflects the behavior and treatment progress of a specific group of people over a limited period of time. As such, any generalizations made regarding the larger dementia population must consider that these results may not be representative of every person that displays VDB. In addition to issues with the inclusion criteria, the investigator was not able to control for the prescribing (i.e., the type of medication, the number of medications, and the dosage of the medications) of psychotropic medication or the use of PRN medications. In retrospective analyses, limitations such as this make it extremely difficult to determine which medication, if any was actually producing the observed effect in the participant's behavior.

Other limitations of this study were the data-gathering instrument and the use of the interdisciplinary progress notes. In regards to the data-gathering instrument, the investigator created his own rating scale so that he could quantify the care provider's subjective observations of the participant's behavior. Scales such as this, although useful, can create the potential for bias, as they have not been proven to be reliable or valid for the construct that they were designed to measure. As to the interdisciplinary progess notes, it is possible that there were several types of errors that occurred during the process of collecting the data. For example, it is possible that a participant exhibited a specific type of behavior (i.e., they were non-disruptive or they exhibited VDB) but the nurse was unable to make an entry in the participant's medical record. It is also possible that the nurse and the other members of the nursing team did not hear a participant at the specific time that they were displaying VDB. In this manner, the participant would be described

as being non-disruptive when in fact they were displaying periods of VDB. Alternatively, it is also possible for nursing staff to be so accustomed to a participant's behavioral presentation that when the participant is actually demonstrating loud and disruptive behavior they are in fact documented as being mostly quiet with intermittent periods of VBD.

CHAPTER FOUR

Method and Procedure

The researcher sought to examine the proposed questions by evaluating the inter-disciplinary progress notes and medication records of 19 participants that exhibited VDB. At the time of the study, all of the participants were deceased or no longer living at the psychiatric institution described below.

Ethical Approval

Ethical approval to conduct this research was obtained from the attending university's health research and ethics board. Upon receiving this approval the principal researcher sought permission to conduct his research at a major psychiatric institution in western Canada. To do so, a copy of the research protocol was submitted to the research and ethics committee that governs the aforementioned institution as well as the manager of the research setting. Both parties approved the research protocol and granted the researcher permission to conduct this study.

Setting

The setting for this study is a major psychiatric institution in western Canada. Within this institution there are four programs that offer in-patient psychiatric services to children, adults and seniors. For the purposes of this study, the researcher was interested in the Seniors Mental Health Program (SMHP). The SMHP is an acute psycho-geriatric program that offers psychiatric services primarily to individuals aged 65 years and older. In rare instances, there are individuals younger than 65 years who have been admitted. The program is comprised of five, 25-bed units, of which three units treat individuals who have been diagnosed with dementia or a similar neuro-degenerative disorder.

Admissions to the program are accepted from a community physician or from a community service provider with the involvement of a physician. Once admitted, a patient receives a full psychiatric assessment, physical examination, nursing assessment, social work assessment (including a detailed social history) and an assessment by a dietician, physiotherapist, pharmacist, occupational therapist, and a psychologist. In most cases, an individual is admitted, assessed, treated and returned to the community facility from which they were admitted within 50 days.

Study Design and Participants

The participants in this study included all persons that were admitted to the three dementia units between June 1, 2003 and April 30, 2008. Participants who stayed less than 100 days were excluded from the study.

A convenience sample was used for this study, as the principal researcher is also an employee of the research setting. Although a convenience sample can create the perception of bias, this study has minimized that potential by investigating a natural cohort. According to Gorwood (2006) naturalistic cohorts have been cited as the best samples when an appropriate sampling frame is not available to randomly select members of a targeted population.

Participant Recruitment

Participants for this study were recruited by first obtaining a list of all the persons who had died or were discharged from the three dementia units between June 1, 2003 and April 30, 2008. In total, there were 353 deaths/discharges. Next, the researcher reviewed each of the individual's medical records and determined whether or not the individual

met the inclusion criteria. Of the 353 potential participants, 19 individuals satisfied the inclusion criteria listed in Table 2.

Table 2: Participant inclusion criteria

Number	*Description*
1	Upon admission to the SMHP, the participant's score on the Mini-Mental Status Exam was 10 or less.
2	The participant had an Axis I DSM-IV TR diagnosis of dementia.
3	The participant was admitted to the SMHP while they displayed VDB or during the course of their admission they developed VDB and displayed the behavior within the 100 days before the day of their death or discharge to another community facility.
4	The participant was a resident of the SMHP for a minimum of 100-days prior to the day of their death or discharge to another community facility.
5	The participant was a resident of the SMHP within the last 5 years.
6	The participant was 60 years of age or older at their time of their admission.

Sample Demographics

The sample in the research study consisted of 9 males and 10 females. The average age at the time of death or discharge was 78.2 years (SD = 8.2). Of the total sample, 10 patients died in hospital, three were discharged secondary to mitigating circumstances and six were discharged without mitigating circumstances. Sixteen participants were non-ambulatory and all participants were fully dependent on nursing staff for their ADLs. One participant was still able to eat independently, while all of the other participants required the assistance of nursing staff. The participant's average MMSE score was 1.7 (SD = 2.4) and the average length of stay was 858.6 days (SD = 707.0). A review of the participant's charts and discharge summaries revealed that nine participants were diagnosed with AD; four participants were diagnosed with mixed dementia; four were diagnosed with VaD; one with DLB and the other participant was diagnosed with FTD. A summary of these data as well as the types of VDB is provided in Table 3. A summary of the participant's concomitant medical conditions and medical procedures is provided in Table 4.

Table 3: Participant demographics

Patient	*Type-VDB*	*MMSE*	*Age*	*Gender*	*Length of Stay*	*Diagnosis*
1	TALK	0	82	Female	420	AD
2	TA/MU	0	85	Male	480	VaD
3	TALK	3	74	Male	261	MIXED
4	SC	0	81	Male	1168	VaD
5	TA/MU	0	79	Female	1912	AD
6	TALK	8	90	Male	321	AD
7	TALK	4	80	Female	600	VaD
8	TA/MU	0	86	Female	291	FTD
9	TA/MU	2	74	Male	517	MIXED
10	TALK	0	73	Male	327	VaD
11	TALK	0	80	Male	2514	AD
12	TALK	0	98	Female	147	MIXED
13	SC	0	62	Female	1335	AD
14	SC	4	78	Female	425	AD
15	SC	5	67	Female	806	AD
16	SC	0	76	Male	2003	AD
17	TA/MU	3	72	Female	300	AD
18	TA/MU	4	73	Male	1708	MIXED
19	SC	0	75	Female	779	DLB

DLB = Dementia with Lewy Bodies
MIXED = Dementia due to Multiple Etiologies
VaD = Vascular Dementia
TALK = Talking-VDB
AD = Dementia of the Alzheimer's Type
FTD = Fronto-Temporal Dementia
SC = Screaming-VDB
TA/MU = Both Talking-VDB & Muttering-VDB

Table 4: Participant clinical characteristics, Axis III diagnoses & medical procedures

Patient	*Ambulation Status*	*Status at Discharge*	*Concomitant medical conditions & medical procedures*
1	Non-Amb	Died	Renal Failure, CHF, Type II Diabetes, Hypertension, Hypothyroidism, Left Cataract Removal with Lens Implant, Glaucoma, Hypertriglyceridema, Angina, Diverticulitis, B12 Deficiency, Intermittent Anemia, ECT
2	Non-Amb	Died	CHF, COPD, TURP, Left Hip Fracture, CVA – Left hemiparesis, Depression
3	Non-Amb	Died	Hypothyroidism, Type II Diabetes, Hypertension, CVA, Glaucoma, History of Gallstones & Kidney Stones
4	Non-Amb	Discharged	Legally Blind, CVA, Renal Tract Malignancy, Hematemesis-ASA-Related, Right Hip Fracture, Allergic Rash, Teeth Extraction
5	Amb	Discharged	COPD, Diverticulitis, Hypothyroidism
6	Non-Amb	Died	Major Depressive Disorder, Chronic Pain, Hypertension, Atrial Fibrillation, TURP, Degenerative disc disease of cervical spine, Left Inguinal Hernia, CHF, UTI, Cataract, Retinal Detachment, ECT
7	Non-Amb	Discharged	Type II Diabetes, PD, CVA, Hypertension Osteoarthritis, Osteoporosis, Iron Deficiency
8	Non-Amb	Died	Seizure Disorder

9	Non-Amb	Died	Prostate Cancer, Angina, Left Inguinal Hernia, Dental Carries
10	Non-Amb	Discharged	Perthes Disease – Hip, CHF, Hearing Impairment, Head Injury
11	Non-Amb	Discharged	Nil
12	Non-Amb	Died	Osteoarthritis, Partial Deafness, Vitamin B12 Deficiency
13	Non-Amb	Discharged	Hypothyroidism, Hypercholesterolemia, Fibromyalgia, Visual Impairment, Teeth Extraction, ECT
14	Non-Amb	Died	Hypertension, Mastectomy, Pulmonary TB, Possible Middle Ear Abnormality
15	Non-Amb	Discharged	Hypothyroidism, History of Headache, Possible History of TIA, Scoliosis, Arthritis, PBA
16	Amb	Discharged	COPD
17	Amb	Died	UTI, Hysterectomy, Varicose Vein Surgery, Depression
18	Non-Amb	Discharged	Bilateral Cataracts, Remote History of Head Injury, Psoriasis, Left-Foot Amputation
19	Non-Amb	Died	Hypothyroidism, Hypotension, Left- Inguinal Hernia, Avascular Necrosis of Right hip, Shingles

Legend:

Amb = Ambulatory	CVA = Cerebral Vascular Accident
CHF – Congestive Heart Failure	UTI = Urinary Tract Infection
COPD = Chronic Obstructive Pulmonary Disease	PD = Parkinson's Disease
TIA = Trans Ischemic Attack	TB = Tuberculosis
TURP = Transurethral Resection of the Prostate	PBA = Pseudobulbar affect

Data Collection

Collection of Data for Vocally Disruptive Behaviour

The setting for this study requires that nursing staff make a legal entry in a patient's chart at least once per nursing shift. Nursing shifts occur from 07:15 – 15:30, 15:30 – 23:45 and 23:45 – 07:15. In general, these entries describe the patient's level of cooperation to medication administration, treatments, nursing assistance and whether or not they exhibited any behavioral and/or psychiatric disturbances.

To assess the participant's level of VDB, the researcher examined the interdisciplinary progress notes of each patient for 100 days prior to the day of their death

or discharge. In total, 300 nursing shifts were coded according to the coding criteria provided in Table 5.

Table 5: Coding criteria for determining the frequency and intensity of vocally disruptive behavior

Number	*Description*
0	No documentation about vocally disruptive behavior.
1	Participant was quiet and/or non-disruptive for the entire shift.
2	Participant was mostly quiet with intermittent periods of vocally disruptive behavior.
3	Participant displayed loud vocally disruptive behavior throughout the entire shift.
4	Participant was extremely loud throughout the entire shift.

Collection of Data for Daily Dosage of Psychotropic Medications

Daily administration of all psychotropic medications, including those administered PRN was recorded from the participant's prescription records by dosage, route and time of administration. The researcher also recorded all the psychotropic medications that the participant was prescribed during the entire duration of their admission. These data, including the participant's medications during the 100 days before the day of their death or discharge are presented in Table 6. If a patient refused their medication or if the nurse withheld their dose, the datum for that specific administration was recorded as zero. If available, the researcher also recorded the reason for the patient's refusal.

Table 6: Summary of prescribed psychotropic medications during the 100 days before the participant's death or discharge as well as during the course of their admission

Participant	*During 100-days*	*During Admission*
1	Zopiclone, Lorazepam, Memantine, Trazodone, Venlafaxine, Risperidone	Paroxetine, Citalopram, Aprazolam
2	Olanzapine, Fluoxetine	Sertraline, Zopiclone, Trazodone, Rivastigmine, Lorazepam
3	Risperidone, Gabapentin, Quetiapine, Zopiclone, Lorazepam	Carbamazepine, Citalopram

4	Lorazepam. Olanzapine, Citalopram	Temazepam, Carbamazepine, Gabapentin Trazodone, Zuclopenthixol, Venlafaxine, Risperidone, Loxapine
5	Clonazepam, Citalopram, Olanzapine, Carbamazepine	Trazodone, Risperidone, Quetiapine, Lorazepam, Valproic Acid, Zopiclone, Gabapentin, Loxapine, Rivastigmine, Benztropine, Venlafaxine
6	Chlorpromazine, Carbamazepine, Memantine, Venlafaxine, Trifluperazine, Zopiclone, Bupropion, Gabapentin, Lorazepam	Nabilone, Doxepin
7	Gabapentin, Trazodone, Lorazepam	Levodopa, Donepezil
8	Valproic acid	Olanzapine, Citalopram, Quetiapine, Zuclopenthixol, Lorazepam
9	Olanzapine, Lorazepam	Olanzapine
10	Fluoxetine, Fluphenthixol	Quetiapine, Citalopram, Benztropine
11	Lorazepam, Trazodone, Carbamazapine	Risperidone, Valproic Acid, Zopiclone, Quetiapine, Benzotropine, Lorazepam, Loxapine, Olanzapine, Sertraline, Clonazepam, Zuclopenthixol, Chlorpromazine, Zaleplon
12	Gabapentin, Lorazepam, Trazodone, Temazepam, Risperidone, Olanzapine, Carbamazepine, Citalopram, Diazepam	
13	Zopiclone, Gabapentin, Amitriptyline	Clozapine, Paroxetine, Olanzapine, Trazodone, Rivastigmine, Benzotropine, Quetiapine, Venlafaxine, Lorazepam, L-Tryptophan
14	Rivastigmine, Zopiclone, Trazodone, Clonazepam	Risperidone, Levodopa, Loxapine, Rivastigmine, Pramipex
15	Oxapam, Citalopram, Amitriptyline, Valproic Acid	Olanzapine, Lorazepam, Gabapentin, Quetiapine, Benztropine, Loxapine
16	Zopiclone	Trazodone, Risperidone, Chlorpromazine, Lorazepam, Valproic Acid, Zuclopenthixol, Donepezil, Quetiapine, Sertraline, Oxapam, Gabapentin, Carbamazapine, Clonazepam, Olanzapine, Citalopram

17	Olanzapine	Donepezil, Citalopram, Trazodone, Rivastigmine, Zopiclone
18	Risperidone, Gabapentin, Quetiapine, Lorazepam	Olanzapine, Citalopram, Carbamazepine
19	Lorazepam, Zopiclone, Gabapentin, Clozapine	Risperidone, Citalopram, Quetiapine, Carbamazepine, Trifluperazine, Chlorpromazine, Loxapine, Diazepam, Cloimpramine, L-Tryptophan, Clonazepam, Melatonin, Trazodone, Levodopa, Propranolol, Bupropion, Mirtazapine, Benzotropine

Figure Caption: All medications are listed by their generic name.

Statistical Procedures/Analysis

The participant's ratings for VDB were combined by gender and dementia diagnosis for each of the three nursing shifts, and analyzed with SPSS 12.0 (Statistical Package for the Social Sciences). In this manner, the researcher was able to compare the rating of VDB emitted by females to that of males as well as by each type of dementia diagnosis. However, because there was only one person with DLB and one person with FTD, the researcher only compared VDB by diagnosis for persons with AD, VaD and mixed dementia. These comparisons were calculated with a univariate analysis of variance (ANOVA). The level of significance for this study was set at $p < .05$ and .001 (please see below).

To determine if there was any change in the ratings of the participant's VDB following the introduction of at least one psychotropic medication, the researcher reviewed the data to determine if there were any psychotropic medications introduced or changed during the 100 days before the day of the participant's death or discharge. In total 10 participants were introduced to a new psychotropic medication or the dosage of their existing psychotropic medication was changed. However, after reviewing this data it was clear that the researcher would not be able to evaluate the participant's rating of

VDB against their prescribed psychotropic medications. The latter was because when a psychotropic medication was introduced, increased or decreased the participant had another psychotropic medication removed, decreased or increased. In other cases, the participant's dosage did not change or the participant was heavily medicated with analgesic medication when their psychotropic medication was discontinued. As such, the researcher could not determine the extent that a specific medication was producing its intended effect. Knowing this, the researcher tallied the medications that were prescribed during the 100 days as well as all of the psychotropic medications that were prescribed during the entire course of the participant's admission. From these data the researcher could determine which medications were the most frequently prescribed as well as those that were most likely to be discontinued. The researcher also grouped the prescribed psychotropics according to their pharmacologic classification so that he could determine which class of psychotropic medication (i.e., antidepressant pharmacotherapy) was the most commonly prescribed.

The researcher then analyzed the data to determine which participants were discharged from the psychiatric institution as well as those that were discharged with or without mitigating circumstances. Of the nine participants that were discharged, two were discharged secondary to having a full dental extraction (i.e., the interdisciplinary progress notes indicated a significant decrease in the participant's VDB) and one was discharged so that he could receive palliative care. In regards to the two participants that had a full dental extraction, the physician concluded that the pain associated with poor dentition was a significant contributor for these participant's VDB. A summary of the mean rating of VDB and the psychotropic medications that the six participants (i.e., discharged

without mitigating circumstances) were prescribed during the 100 days is presented in Table 7. The researcher also compared the mean length of stay for those that were discharged without mitigating circumstances to those who died in hospital and those who were discharge secondary to mitigating circumstances. With the latter information it would be possible to determine if disease progression (i.e., length of stay) had any effect on the participant's likelihood of being discharged. These results are presented in Chapter five.

Table 7: Summary of the participants that were discharged to another community facility without mitigating circumstances

Patient	*Day Shift VDB*	*Evening Shift VDB*	*Night Shift VDB*	Psychotropic medications
#5	1.52 (SD = 0.59)	1.55 (SD = 0.72)	0.11 (SD = 0.53)	Clonazepam, Citalopram, Olanzapine, Carbamazepine
#7	1.30 (SD = 0.50)	1.20 (SD = 0.40)	0.10 (SD = 0.44)	Gabapentin, Trazodone, Lorazepam
#11	1.27 (SD = 0.45)	1.32 (SD = 0.53)	0.02 (SD = 0.20)	Lorazepam, Trazodone, Carbamazapine
#15	1.00 (SD = 0.00)	1.01 (SD = 0.10)	0.00 (SD = 0.00)	Oxapam, Citalopram, Amitriptyline, Valproic Acid
#16	1.79 (SD = 0.41)	1.89 (SD = 0.35)	0.06 (SD = 0.34)	Zopiclone
#18	1.97 (SD = 0.17)	1.97 (SD = 0.17)	0.00 (SD = 0.00	Risperidone, Gabapentin, Quetiapine, Lorazepam

CHAPTER FIVE

Findings and Results

Using SPSS 12.0 the mean scores were calculated for both genders at three different times (i.e., day shift, evening shift and night shift). The statistical significance of the differences between these means was examined with a univariate ANOVA.

Tests of Hypothesis

Null hypothesis 1:There will be no reported differences in the rating of vocally disruptive behaviour for males versus females.

Null Hypothesis 2: There will be no reported differences in the rating of vocally disruptive behaviour for the participants with different diagnoses.

Table 8: Difference in the rating of vocally disruptive behavior for males and females

Gender	Mean Rating by Nursing Shift		
	Days (N = 100)	Evenings (N = 100)	Nights (N = 100)
Male	1.72 (SD = 0.80)	1.80 (SD = 1.06)	0.22 (SD = 0.68)
Female	1.85 (SD = 0.76)	1.96 (SD = 0.79)	0.44 (SD = 0.79)
Significance (Time)	$F = 47.224_{(2,57)}$, $p < 0.01$*		
Significance (Gender)	$F = 1.270_{(1,57)}$, $p < 0.265$		
Significance (Gender X Time)	$F = 0.039_{(2,57)}$, $p < 0.962$		

*Denotes significance at the $\alpha = .05$ level.

Table 9: Post hoc analysis of the differences in the rating of vocally disruptive behavior over time

Time	Day Shift	Evening Shift	Night Shift
Day Shift	0	-0.0895	1.4595*
Evening Shift	0.0895	0	1.5489*
Night Shift	-1.4595*	-1.5489*	0

* Post hoc analysis was completed with the Tukey method.
*Denotes significance at the $\alpha = .05$ level.

Similarly, the mean scores were calculated for the three dementia diagnoses at three different times (see above). The statistical significance of the differences between these means was examined with a univariate ANOVA.

Referring to Table 8, it appears that there was no significant difference between the ratings of VDB for males and females and that this trend was consistent over time. Alternatively, referring to Table 10, the results suggest that there was a significant difference between the mean rating of VDB and the type of dementia diagnosis. Post hoc analysis indicated that the participants who were diagnosed with mixed dementia were

Table 10: Difference in the rating of vocally disruptive behavior and dementia diagnosis

Diagnosis	Mean Rating by Nursing Shift		
	Days	Evenings	Nights
AD (N = 9)	1.55 (SD = 0.43)	1.66 (SD = 0.57)	0.23 (SD = 0.43)
VaD (N = 4)	1.74 (SD = 0.64)	1.73 (SD = 0.66)	0.28 (SD = 0.25)
Mixed (N = 4)	2.10 (SD = 0.48)	2.24 (SD = 0.49)	0.67 (SD = 0.55)
Significance (Diagnosis)	$F = 4.589_{(2,42)}$, $p < 0.016$*		
Significance (Diagnosis x Time)	$F = 0.060_{(4,42)}$, $p < 0.993$		

*Denotes significance at the $\alpha = .05$ level.

Table 11: Post hoc analysis of the differences in the mean rating of vocally disruptive behavior and dementia diagnosis

Diagnosis	AD	VaD	Mixed
AD	0	-0.1046	-0.5246*
VaD	0.1046	0	-0.4200
Mixed	0.5246*	0.4200	0

* Post hoc analysis was completed with the Tukey method.
*Denotes significance at the $\alpha = .05$ level.

rated as significantly higher for VDB than were the participants that were diagnosed with AD. No significant difference was observed between any of the other types of dementia. The results also indicate that there was a significant difference between the rating of VDB and the time of day, whereby the participant's level of VDB during the day and

evening shift was rated as significantly higher than during the night shift. There was no significant difference between the day and evening shift. Based on the above, the first null hypothesis is supported, while the second is rejected.

Null hypothesis 3: There will be no reported change in the rating of the participant's vocally disruptive behaviour following the introduction of any psychotropic medications.

In total, the participants of this study were prescribed 41 different psychotropic medications (see Table 12). Of these medications, zopiclone and zaleplon were prescribed for insomnia and were not used as a means of controlling VDB. Based on the collected data, it would appear that during the entire course of the participant's admission lorazepam was the most frequently prescribed psychotropic medication. Upon further review, it would also appear that of the 10 most commonly prescribed medications, quetiapine, citalopram and rivastigmine were the most likely to be discontinued, whereas gabapentin, lorazepam and olanzapine were the least likely to be discontinued. For a further review of these data please see Table 12.

Continuing with the above, the researcher grouped all of the prescribed psychotropic medications into their pharmacological categories. Using these data, the results indicate that antidepressant pharmacotherapy was the most frequently prescribed psychotropic treatment. The second most frequently prescribed treatment was antipsychotic pharmacotherapy, followed by benzodiazepine pharmacotherapy and mood stabilizer pharmacotherapy (see Table 13 for a summary).

Referring to Table 7, the results indicate that the participant who was discharged with the highest mean (1.97, SD = 0.17) rating of day shift VDB was prescribed risperidone, gabapentin, quetiapine, and lorazepam. It means that his vocalisations ranged

Table 12: Summary of the prescribed psychotropic medications

Psychotropic Medication	*Number of participants that received during their last 100-days & Percentage*	*Number of participants that received during their admission & Percentage*	*Number of participants that had the specific medication discontinued*
Lorazepam	10 (52.63%)	17 (89.47%)	7
Olanzapine	6 (31.58%)	13 (68.42%)	7
Trazodone	5 (26.32%)	12 (63.16%)	7
Citalopram	4 (21.05%)	12 (63.16%)	8
Zopiclone	7 (36.84%)	11 (57.89%)	4
Gabapentin	7 (36.84%)	11 (57.89%)	4
Risperidone	4 (21.05%)	10 (52.63%)	6
Quetiapine	2 (10.53%)	10 (52.63%)	8
Carbamazepine	4 (21.05%)	9 (47.37%)	5
Rivastigmine	1 (5.26%)	6 (31.58%)	5
Loxapine	0 (0.00%)	6 (31.58%)	6
Benzotropine	0 (0.00%)	6 (31.58%)	6
Venlafaxine	2 (10.53%)	5 (26.32%)	3
Clonazepam	2 (10.53%)	5 (26.32%)	3
Valproic acid	2 (10.53%)	5 (26.32%)	3
Chlorpromazine	1 (5.26%)	4 (21.05%)	3
Zuclopenthixol	0 (0.00%)	4 (21.05%)	4
Donepezil	0 (0.00%)	3 (15.79%)	3
Sertraline	0 (0.00%)	3 (15.79%)	3
Levodopa	0 (0.00%)	3 (15.79%)	3
Memantine	2 (10.53%)	2 (10.53%)	0
Fluoxetine	2 (10.53%)	2 (10.53%)	0
Amitriptyline	2 (10.53%)	2 (10.53%)	0
Trifluperazine	1 (5.26%)	2 (10.53%)	1
Bupropion	1 (5.26%)	2 (10.53%)	1
Temazepam	1 (5.26%)	2 (10.53%)	1
Diazepam	1 (5.26%)	2 (10.53%)	1
Oxapam	1 (5.26%)	2 (10.53%)	1
Clozapine	1 (5.26%)	2 (10.53%)	1
Paroxetine	0 (0.00%)	2 (10.53%)	2
L- Tryptophan	0 (0.00%)	2 (10.53%)	2
Fluphenthixol	1 (5.26%)	1 (5.26%)	0
Aprazolam	0 (0.00%)	1 (5.26%)	1
Nabilone	0 (0.00%)	1 (5.26%)	1
Doxepin	0 (0.00%)	1 (5.26%)	1
Melatonin	0 (0.00%)	1 (5.26%)	1
Propranolol	0 (0.00%)	1 (5.26%)	1
Mirtazapine	0 (0.00%)	1 (5.26%)	1
Cloimpramine	0 (0.00%)	1 (5.26%)	1
Zaleplon	0 (0.00%)	1 (5.26%)	1
Pramipex	0 (0.00%)	1 (5.26%)	1

* Percentage is based on the entire sample. Example – Lorazepam {10 (Participants that received Lorazepam during the 100 days) / 19 (Total sample)} x 100.

from being quiet and/or non-disruptive for the entire shift to displaying loud vocally disruptive behavior throughout the entire shift. This participant's length of stay was 1708 days. He was diagnosed with mixed dementia. The participant with the second highest rating of day shift VDB was participant #16. He was diagnosed with AD. His mean rating of VDB was 1.79, SD = 0.41 and his length of stay was 2003 days. VDB was rated to be the same as participant #18. Other than zopiclone, participant #16 was not prescribed any psychotropic medication.

Table 13: Summary of different classes of psychotropic medications that were prescribed during the course of the participant's admission

Psychotropic Medication Class	*Number Psychotropic Medications that were Prescribed & Percentage*
Antidepressant	11 (26.83%)
Antipsychotic	9 (21.95%)
Benzodiazepine	6 (14.63%)
Mood Stabilizer (Anticonvulsant)	3 (7.32%)
Cognitive Enhancers	3 (7.32%)
Beta Blockers	1 (2.44%)
Other*	8 (19.51)

* Includes medications for insomnia, neurotransmitter precursors and pharmacological treatments whose properties enable them to act as psychotropics.

Oxapam, citalopram, amitriptyline, and valproic acid were prescribed to the participant (i.e., #15) with the lowest rating of day shift VDB. This participant was diagnosed with AD. Her length of stay was 806 days. The participant that was diagnosed with VaD was prescribed clonazepam, citalopram, olanzapine, and carbamazepine. Her length of stay was 600 days and her average rating of day shift VDB was 1.30 (SD =

0.50). The findings indicate that during the day her vocalisations ranged from being quiet and/or non-disruptive for the entire shift to being mostly quiet with intermittent periods of VDB. The mean rating of day shift VDB for participant #7 was similar to that of participant #11. Participant #7 was prescribed gabapentin, trazodone, and lorazepam, while participant #11 was prescribed lorazepam, trazodone, and carbamazapine.

Continuing, the researcher compared the mean length of stay for those who were discharged without mitigating circumstances to those who died in hospital and those who were discharged secondary to mitigating circumstances. The results indicate that those who were discharged without mitigating circumstances stayed in the hospital significantly longer, $F = 18.60_{(1,17)}$, $P < 0.001$, than those that died in hospital or those that were discharged secondary to mitigating factors. The average length of stay for those who were discharged without mitigating circumstances was 1590.50 days (SD = 739.83), while for those who died in hospital or were discharged secondary to mitigating circumstances the average of their length of stay was 520.85 days, (SD = 360.06).

Based on the above findings, it cannot be concluded that there was a significant difference in levels of exhibited VDB with the introduction of any one specific psychotropic medication. As such, the third null hypothesis can be neither supported nor rejected (see discussion).

CHAPTER SIX

DISCUSSIONS AND CONCLUSIONS

Summary of the Literature

Dementia refers to a collection of neuro-degenerative disorders that are characterized by the development of multiple cognitive deficits. These deficits can be the result of the direct physiological effects of a general medical condition, the persisting effects of substance abuse or be of multiple etiologies. As such disorders progress, cognitive impairments become more invasive, functional abilities decline and the BPSD become more problematic and difficult for caregivers to manage (American Psychiatric Association, 2000). To date, the most commonly diagnosed types of dementia are AD, VaD, DLB and FTD and of these, AD is the most prevalent (see Herrmann & Lanctôt, 2007; Levy & Chelune, 2007).

In Canada it has been estimated that by 2011, there will be 111,560 new cases of dementia per year (The Alzheimer's Society of Canada, 2006) and 215,847 new cases per year by 2031 (Gautrin et al., 1990). In addition, the research has suggested that each person who is diagnosed with dementia will experience at least one type of BPSD during the course of his or her illness (Herrmann & Lanctôt, 2007). At present, the growing dementia population has been labeled one of the greatest public health concerns of our time (Hemels et al., 2001) and as these numbers continue to increase it is likely that the number of people that will display with treatment-resistant BPSD will also increase (Herrmann & Lanctôt, 2007). Considering that such individuals are usually admitted to psychiatric institutions and that most individuals do not leave (Neville & Byrne, 2007) it

is likely that in addition to increased healthcare expenditure, the growing dementia population will also minimize general access to psychiatric hospitals.

The BPSD are common and serious complications of dementia that are not only difficult to manage, but in many cases are also resistant to treatment. They are evident in all types of dementia and their presence varies as a function of the disease's progression (Schreinzer et al., 2005). Of all the BPSD, one of the most distressing and probably the most difficult to treat is VBD (Sloane et al., 1997). In general, VDB refers to any sound that when uttered is out of the ordinary for a specific situation. It creates a significant amount of stress for the individual and it threatens the quality of interpersonal relationships with family and caregivers. Prevalence rates range from 11 to 30 percent (i.e., once the behavior is differentiated from agitation) for most community and institutionalized settings (Burgio et al., 2001) and it appears that such behaviors are similar across different cultures (see American Psychiatric Association, 2000). It also seems that most individuals who exhibit VDB are inconsolable and that many demonstrate such heightened levels of disruption that they are restricted from communal areas, often spending the majority of their waking hours in isolation (see Barton et al., 2005; Nagaratnam & Nagaratnam, 2005).

As with other BPSD, vocally disruptive behavior is assumed to have multiple etiologies (Meares & Draper, 1999). Studies indicate that severity of cognitive impairment (Nagaratnam et al., 2003), inability to perform activities of daily living (CohenMansfield & Werner, 1997), depression (Dwyer & Byrne, 2000), pain (Manfredi et al., 2003) and an inability to communicate (Matteau et al., 2003) are probable causes of VDB. Other associations include: psychosis (Finkel, 2003); gout (Liu et al., 2000);

inability to cope with stress (Ragneskog et al., 1998); environmental factors (Groulx, 2004); the behavior of caregivers (Babbage, 2005); constipation (Kopala & Honer, 1997); and delirium (Johnson, 1990). Finally, the research suggests that vocally disruptive behavior is not unique to one type of dementia and that each type is equally as likely to demonstrate the behavior (Meares & Draper, 1999; CohenMansfield et al., 2003).

After reviewing the available literature on VDB, the research suggests that there have been no treatments proven to be effective in all, or even most cases. Furthermore, the consensus in research findings suggests that the treatment of VDB as well as other BPSD should be multifaceted and that it must include a medical, environmental and behavioral assessment. Once a person has been assessed the research indicates that first-line interventions should be non-pharmacological. If the non-pharmacological intervention is unsuccessful and if pharmacotherapy is necessary, the medication should be started at the lowest possible dose. Furthermore, once the patient has shown a favorable response for a specific period of time the physician should make every effort to reduce the dose and if possible to discontinue the medication completely. Finally, whenever considering the use of a psychotropic medication the choice of medication should always be based on the agent's pharmacological characteristics and how those characteristics will effect a patient's existing medical condition(s) and/or interact with their concomitant medications (Herrmann & Lanctôt, 2007).

After conducting a systematic review of the available literature, the research also suggests that even though there is evidence to support the use of non-pharmacological interventions, most benefit from these interventions has been with individuals who experience mild and moderate dementia. For individuals with severe dementia non-

pharmacological interventions have minimal effect and in most cases do little to reduce the intensity and/or frequency of their vocal disruption. To that end, the mainstay for treating VDB has been pharmacotherapy. In extreme cases ECT has been used, but as a rule most alternative decision-makers prefer the use of pharmacotherapy (Snowdon et al., 1994).

To date, antipsychotics, antidepressants, anticonvulsants, anxiolytics, beta-blockers, cognitive enhancers, buspirones and other types pharmacological agents have been used to treat the BPSD (Herrmann & Lanctôt, 2007). However, after reviewing the available literature the same could not be said for the treatment of VDB. According to the available literature transdermal nicotine, trazodone, citalopram, paroxetine, and risperidone have been investigated. Each intervention has been shown to be capable of reducing VDB, but because most of these studies are single or two participant designs it is difficult to generalize these findings to the larger dementia population (Kopala & Honer, 1997). Furthermore, part of the reason for the lack of research with individuals that display VDB is that VDB is not addressed as a specific behavioral disturbance. Instead, the research has focused on the broader term of agitation and investigated clusters of BPSD as opposed to individual behaviors (Robert & Allain, 2001). For these reasons, amongst others, there is insufficient evidence to recommend either of the aforementioned interventions as a treatment for VDB.

This study investigated the psychotropic treatment of 19 participants with severe dementia that displayed VDB. The setting for this study was an acute psycho-geriatric program that offers psychiatric services to individuals aged 65 years and older. The program is comprised of five, 25-bed units, of which three units treat individuals who

have been diagnosed with dementia or a similar neuro-degenerative disorder. In total, 353 people died or where discharged to another community facility between June 1, 2003 and April 30, 2008. The purpose of this study was to determine which psychotropic medications, if any were associated with reductions in the participant's rating of VDB during the course of the 100 days before the day of their death or discharge. A second purpose of this study was to propose a neurological/cognitive model that integrated the neurotransmitter abnormalities of dementia with the neural circuitry of human vocalisation. With this information, it was hoped that the present study would provide clinicians and other health care providers with a better understanding of why some psychotropic medications are beneficial for treating VDB and why others are not.

In regards to the neurological/cognitive model the researcher has proposed that VDB develops as a result of specific alterations (i.e., neurochemical and/or neuroanatomical) to the pathways and anatomical brain areas that interconnect the cerebral cortex, the mediofrontal cortex, the basal ganglia, the cerebellum, and the PAG with the phonatory motoneurons. These changes are believed to occur as a progressive process (albeit simultaneous dysfunction is also possible) whereby alteration to the voluntary speech structures (i.e., the substructures of the basal ganglia and/or the cerebellum) would occur first and be followed by neuronal dysfunction of the neuroanatomical areas that facilitate involuntary speech (i.e., the PAG). With time and as the illness progresses, the voluntary control over the substructures of the basal ganglia and the cerebellum would deteriorate and in doing so the cerebral cortex and the mediofrontal cortex would no longer be capable of generating and/or relaying appropriate neural messages to the phonatory motoneurons. At this point in the illness, most, if not all

vocalization would be the result of involuntary (i.e., visceromotor) speech that is facilitated by the PAG. As the individual continues to deteriorate it is assumed that the PAG will also experience neuronal dysfunction (i.e., atrophy or neuronal changes secondary to an ischemic event) and that as a result there will be specific alterations to the initiation and/or control of involuntary speech (Schultz et al., 2005).

Based on the above, the proposed model would suggest that during the course of pathological brain atrophy, talking-VDB would develop first and be followed by muttering-VDB, singing-VDB, and lastly by screaming-VDB. In this manner, talking-VDB would exhibit the most control over the ability to speak, whereas a person that exhibits screaming-VDB would have no and/or minimal control. As such, the proposed model has suggested that the person who mutters and/or sings would experience neuronal deterioration that is more severe than talking-VDB but less severe than a person that exhibits screaming-VDB.

Summary of the Findings & Conclusions

Based on the results, it appears that 10 of the 19 participants died in hospital and that the 6 participants who where discharged without mitigating circumstances stayed in hospital significantly longer than were those who died in hospital or those who were discharged secondary to mitigating circumstances. Not only do these data suggest that individuals who display VDB remain in hospital for extended periods of time and that these individuals show poor response to pharmacological intervention but it also reiterates the difficulty of treating an elderly client, especially one that is suffering from dementia. Most participants (see Table 4) in this study had numerous concomitant medical illnesses and it appears that for some of these participants, such illnesses had a

pronounced effect on their behavioral presentation. For example, participant #19 was diagnosed with an avascular necrosis of the right hip, participant #6 was diagnosed with chronic pain and degenerative disc disease and participants #4 and #13 both received a full dental extraction. In addition to the issues with the teeth, participant #4 had renal tract malignancy and participant #13 was also diagnosed with fibromyalgia. The VDB of participant #4 and #13 improved considerably following their dental extraction and both participant #6 and #19 exhibited ratings of VDB that were higher than most of the other participants. Taken together, these findings are congruent with the available research and the findings emphasize the importance of a multifaceted approach to treating a person with dementia.

The findings of this study also show that there was no significant difference between the two genders and the rating of VDB. These results were expected, but since depression has been speculated to be an underlying cause of VDB (see Greenwald et al., 1986; Kim et al., 2000; Ramadan et al., 2000) and since women experience depression more often than men (American Psychiatric Association, 2000), one might assume that VDB would be more prevalent in women. According to the findings of this study, the latter does not seem to be the case, although the findings of this study must be interpreted with caution, since the total sample was comprised of only 19 participants. In this regard, future research into the association between gender and VDB seems to be warranted.

In regards to dementia diagnosis, this study did find a significant difference between the rating of VDB for the participants that were diagnosed with AD and mixed dementia. In this sample, participants who were diagnosed with mixed dementia received significantly higher ratings of VDB than the participants diagnosed with AD. The data

did not show any difference between the mean rating of VDB for participants with AD and VaD. In this regard, it is possible that the combined pathologies of AD and VaD (i.e., mixed dementia) have created such an alteration to the neural pathways that regulate speech that an individual experiences a more pronounced level of neuroanatomical dysfunction. For example, in addition to experiencing the cerebral atrophy that is characteristic of AD a person with mixed dementia may also experience ischemic events anywhere within the brain. In regards to VDB, such ischemic events may occur within the basal ganglia, cerebellum, PAG, mediofrontal cortex or within any of the neuronal pathways that connect these structures. In the study, by CohenMansfield et al. (2003), the author's did not specifically evaluate individuals with mixed dementia, although it was reported that participants with VaD demonstrated more speech abnormalities than the participants that were diagnosed with AD. These findings are congruent with the results of this study, as 75% (i.e., 3 out 4) participants with mixed dementia demonstrated a mixture of talking and muttering-VDB, whereas only 22% (2 out of 9) of the participants with AD exhibited a mixture of talking/muttering-VDB. Participants that were diagnosed with VaD exhibited talking-VDB, screaming-VDB, and a mixture of talking and muttering-VDB. Collectively, these data suggest that the presentation of VDB could be related to the type of dementia diagnosis and that because of this possibility, accurately diagnosing the individual's pathology is an important consideration when evaluating and treating VDB. Having said that, it is also important to note that the sample size for this study was small and that this investigation will need to be replicated with a larger sample and should include more participants who are diagnosed with DLB and FTD.

This study has also found that there was no significant difference between the rating of VDB for the day shift and the evening shift and that both of these time intervals were significantly different from the ratings during the night shift. After reviewing the data, it appears that the latter condition occurred because the participants slept through the entire night as opposed to lying quietly awake in their beds. Comparing the findings of this study with those of Burgio et al. (2001) the mean ratings of VDB by nursing shift for this study are congruent with findings in previous research. While investigating 68 participants with VDB, Burgio et al. (2001) discovered that there was a cubic trend for the temporal presentation of VDB. The authors noted that participants exhibited high levels of VDB from 1- 4 P.M., less VDB from 4 – 7 P.M. and high levels again from 7 – 8 P.M. As mentioned above, day shift covers 07:00 – 15:30 and evening shift covers 15:30 – 23:45. According to the information provided by Burgio et al. (2001), participants would be expected to display approximately 2.5 hours of disruptive VDB during the day shift and 1.5 hours of disruptive VDB during the evening shift. These projections are congruent with the findings of this study, although it is important to note that many of the participants of this study were noted to display VDB while they were being assisted with their supper meal. According to Burgio et al. (2001), the evening VDB was likely a result of sundowning, while they were unable to explain the 1 p.m. levels of VDB. One explanation for this phenomenon is the possibility that some cases of VDB might occur as a non-ambulatory manifestation of wandering (see Staedt & Stoppe, 2005; Meguro et al, 2004). In this regard, it is possible that the agitation that is created from the inability to process environmental stimuli (i.e., this agitation would normally be displayed as wandering) is thus expressed as VDB.

As discussed above, the researcher was unable to determine which psychotropic medications were associated with reductions in the participant's rating of VDB. However, after tallying all of the prescribed psychotropic medications it appears that of the 10 most commonly prescribed medications, quetiapine, citalopram and rivastigmine were the most likely to be discontinued, whereas trazodone, gabapentin, lorazepam and olanzapine were the least likely to be discontinued. Although the reason why these medications were discontinued was not explicitly stated, it is a general rule in clinical practice that medications are discontinued for the following reasons: 1) the medication is not effective; 2) the medication created intolerable adverse effects; 3) the patient's physical condition was such (i.e., deterioration) that it warranted the medication's discontinuation (see Herrmann 2001; Herrmann & Lanctôt, 2007). As mentioned above, the third reason was quite evident in this study as over half of the sample died in hospital and as shown in Table 4, most individuals had numerous concomitant medical complications. Although, it cannot be determined which psychotropic medication was effective in reducing VDB, the findings did indicate that of all of the prescribed medications, antidepressant pharmacotherapy was the most frequently prescribed course of treatment. The second most frequently prescribed treatment was antipsychotic pharmacotherapy, followed by benzodiazepine and mood stabilizer pharmacotherapy. Based on findings in the literature, it appears that the treatments that were prescribed to these participants were congruent with what is supported by the research (see Herrmann 2001; Herrmann & Lanctôt, 2007).

In addition to the above, the six participants who were discharged without mitigating circumstances represent the most plausible account of the effect that psychotropic medications have on the presentation of VDB. Unfortunately the dosage of

these participant's medications did not change during the 100 days before the day of their death or discharge. As such, the researcher could not determine if any of the prescribed medications had an effect on the participant's demonstration of VDB. In this regard, the researcher was unable to determine what was responsible for the differences in the participant's ratings of day shift VDB (see Table 14). However, the medications that where prescribed to these individuals in the 100 days before their day of discharge represents the medications with the highest level of anecdotal success for being associated with reductions in VDB. In other words, the participant's VDB was such that they could be managed by a community facility. These medications included risperidone, gabapentin, quetiapine, lorazepam, oxapam, citalopram, amitriptyline, valproic acid, carbamazepine, clonazepam, olanzapine, and trazodone. It would also appear that in this group antidepressant, benzodiazepine, and mood stabilizer pharmacotherapy were the most frequently prescribed and/or tolerate pharmacotherapy. These medications will be discussed below in the context of the proposed neurological/cognitive model.

After reviewing the collected data, there is some validity to the proposed model as a possible explanation for the presentation of VDB. Of the six participants that were discharged without mitigating circumstances and displayed screaming-VDB, four were diagnosed with AD. According to the model, individuals that are diagnosed with AD would be the mostly likely to develop screaming-VDB. In this regard, it is the researcher's opinion that the screaming-like behavior that is associated with screaming-VDB is a result of the neuritic plaques and neurofibrillary tangles that occur in the PAG of people that are diagnosed with AD (see Parvizi, 2000). Furthermore, by examining the other participants that were diagnosed with AD, the results indicate that there were three

participants that displayed talking-VDB and two participants with displayed a mixture of talking/muttering-VDB. In this regard, the model suggests that this presentation is a result of the gradual deterioration of the neural pathways that connects the substructures of the basal ganglia and the cerebellum with the mediofrontal and cerebral cortexes. In addition, the participants who were diagnosed with mixed dementia demonstrated either talking-VDB or a mixture of talking/muttering-VDB, while the participants that were diagnosed with VaD, exhibited talking, screaming and a mixture of both talking/muttering-VDB. In this regard, it is likely that the participant that was diagnosed with VaD and displayed screaming-VDB had an ischemic event in the area of the PAG, whereas the other participants with VaD and mixed dementia did not. Furthermore, one would expect that the VDB that was exhibited by these individuals were caused by an ischemic event and/or brain atrophy (i.e., those with mixed dementia) within the neural pathways that connect the mediofrontal cortex with the basal ganglia and the cerebellum. In addition, the participant that was diagnosed with DLB also exhibited screaming-VDB, which could be explained by the formation of senile plaques in the PAG. According to the research by Ballard et al. (2006), individuals with DLB can also developed senile plaques and neurofibrillary tangles.

Based on the above, the proposed model suggests that medications that act on the PAG would be the most efficacious for treating screaming-VDB. Alternatively, medications that affect the basal ganglia, cerebellum, the mediofrontal and cerebral cortexes would be the most beneficial for talking, muttering, and any combination of these two presentations.

Using the data from the six participants that were discharged without mitigating circumstances, it would appear that the pharmacological effect of the prescribed medications would have most likely occurred within the neural circuitry of the basal ganglia, cerebellum, and the mediofrontal cortex. In other words, the participant that exhibited screaming-VDB was not prescribed any psychotropic medications and according to the model the PAG would not be dysfunctional in the remaining participants. In this regard, the benzodiazepines (i.e., lorazepam, clonazepam & oxapam) and mood stabilizers (i.e., gabapentin, CBZ and valproic acid) that were prescribed may have increased the inhibitory effect of GABA or blocked the effect of Glu within the basal ganglia, cerebellum or the mediofrontal cortex. It is also possible that these agents caused an increase in CNS serotonergic functioning. However, because each of these medications differs slightly in their pharmacologic profile and because their pharmacological mode of action is still being investigated (see CPS, 2006) it cannot be determined which of these medications would be preferential over the other as a treatment for VDB.

In regards, to medications that effect 5-HT (i.e., citalopram, trazodone and amitriptyline) and to a certain extent risperidone, olanzapine and quetiapine, the results of this study suggest that medications that modulate serotonergic function and/or neurotransmission are associated with manageable presentations of VDB. In this regard, the research has shown that 5-HT effects the GABAergic interneurons of the deep nuclei of the cerebellum as well as the serotonergic neurons in the striatum of the basal ganglia (see Schweighofer et al., 2003; Lindenmayer, 2000). In this regard, it is possible that the improved serotonergic neurotransmission improved the activation of the GABAergic

interneurons in the cerebellum, which according to the proposed model would reduce the excitatory input to the thalamus and thereby the cerebral cortex (i.e., primary motor cortex). If the effect was in the basal ganglia, one possible mechanism of action could be through the striatum, whereby the improved serotonergic neurotransmission would improve its ability to release or impose inhibition on the thalamus and thereby the cerebral cortex. It should also be acknowledged that in addition to its serotonergic re-uptake inhibitor properties, amitriptyline has an equivalent affinity for NE (i.e., amitriptyline is a TCA). In this regard, it is possible that by inhibiting the re-uptake of NE, amitriptyline was able to improve noradrenergic input to the cerebellum from the VTA and LC (see Grijalba et al., 1994).

In regards to the medications that affected DA (i.e., risperidone, olanzapine & quetiapine) there are several possibilities that may account for the treatment response of these participants. Both participants that were prescribed an antipsychotic displayed a mixture of talking/muttering-VDB, which according to the proposed model would be a result of dysfunction to the neural circuitry that interconnects the basal ganglia and the cerebellum with the mediofrontal and cerebral cortexes. In this regard, it is possible that by blocking dopamine at the D_2 receptor, these medications are in effect regulating the excitatory influence of the substantia nigra on the striatum and by association the thalamus and cerebral cortex. In addition, these medications also have a pronounced effect on the 5-HT_{2A} receptors, which suggests that their effect on VDB may be through a serotonergic mechanism as opposed to dopaminergic. In this regard and after considering the explanation given above, it is possible that these medications produced their therapeutic effect by increasing the arousal in the neocortex (see Meguro et al., 2004). In

doing so, it is possible that the increased arousal facilitated the neurochemical communication between the basal ganglia, cerebellum, mediofrontal cortex and the phonatory motoneurons.

Based on the above it would seem that atypical antipsychotic medications are reasonable treatments for the presentation of talking and muttering-VDB. However, after reviewing the findings from this study as well as the available literature on the PAG, it seems that the benzodiazepines, antidepressants and mood-stabilizers are the most reasonable choices for treating screaming-VDB. Having said that, it is also important to note that previous research by Kopala & Honer (1997) has established that risperidone is associated with reductions in VDB and that atypical antipsychotics are routinely used to treated agitation and other BPSD (see Frenchman 2005; Herrmann & Lanctôt, 2007). In this regard, it is possible that the therapeutic effect of antipsychotic pharmacotherapy is derived from their ability to stimulate the neocortex (see Meguro et al., 2004) or it is possible that the effect is secondary to sedation (see Herrmann & Lanctôt, 2007). If the former is the case, agents such as risperidone, olanzapine, quetiapine, nicotine and psychomotor stimulants (i.e., methylphenidate) may be beneficial for ameliorating screaming-VDB as these agents have the ability to stimulate the neocortex (see Meguro et al., 2004; CPS, 2006). Furthermore, it is also possible that the reduction in VDB following antipsychotic pharmacotherapy is the result of the ability of these agents to influence serotonergic neurotransmission (Kopala & Honer, 1997). The later seems to be a plausible explanation, as the research has shown that both 5-HT and GABA (i.e., serotonergic innervation of GABAergic interneurons) are two of the primary neurotransmitters of the PAG. In either case and after reviewing the available research, it

would appear that more research on the antipsychotic treatment of screaming-VDB is needed.

Having reviewed the above and the available literature, it is clear that we have much to learn about the presentation and treatment of VDB. The research suggests that non-pharmacological interventions should be used first and that if pharmacotherapy is necessary it should be started at the lowest possible dose. Furthermore, antipsychotic pharmacotherapy is not supported by Health Canada as a treatment for the BPSD and the research suggests that benzodiazepines should only be used PRN (see Herrmann & Lanctôt, 2007). By reviewing the information provided in Table 7, it is clear that both typical and atypical antipsychotics were routinely prescribed to these participants and that benzodiazepines were prescribed as regular medications as opposed to PRN. It is also important to note that there was no mention of using non-pharmacological interventions. Despite this information, the present study would suggest that individuals that display talking and muttering-VDB might respond best to antidepressant, antipsychotic, benzodiazepine and mood-stabilizer pharmacotherapy, while the antipsychotic treatment of screaming-VDB would appear to require further investigation.

Before concluding, it is important to reiterate that the length of disease progression appears to be a significant factor in the presentation of VDB. Based on the collected data and the information that was in the participant's interdisciplinary progress notes, it appears that some individuals displayed VDB for a long period of time and as their illness progressed their behavior decreased to the point where they were manageable for a community facility. Although it cannot be said with certainty, it appears that in most cases this effect occurred regardless of the prescribed medications. In this regard, future

research will be needed if we are to determine whether the treatments we provide are significantly beneficial for reducing VDB or if in fact it is the disease's progression (i.e., continued brain deterioration) that is responsible for the participant's manageable presentation. Having said that, it is also important to note that medications that effect ACh and Glu have not been sufficiently studied in populations that display VDB. Considering that both neurotransmitters are excitatory and that both are used extensively by the structures in the proposed model, it is possible that medications that influence these neurotransmitter systems would be beneficial for alleviating VDB. On a similar note, the participants of this study were prescribed few medications that have a significant effect on NE activity. Since NE is involved in the regulation of arousal, agitation, anxiety, and emotion (see Herrmann et al., 2004) and since it is a neurotransmitter of the PAG (Behbehani, 1995), it is possible that medications that effect noradrenergic activity would also be beneficial as a treatment for screaming-VDB. The later, as well as the medications that affect ACh (i.e., rivastigmine) and Glu (i.e., memantine) will require further inquiry if we are to provide treatment recommendations that effectively manage this distressing and treatment resistant BPSD.

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